

FILE 'HOME' ENTERED AT 22:31:56 ON 27 SEP 2007

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FULL ESTIMATED COST

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FILE 'REGISTRY' ENTERED AT 22:32:09 ON 27 SEP 2007

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STRUCTURE FILE UPDATES: 26 SEP 2007 HIGHEST RN 948239-70-1

DICTIONARY FILE UPDATES: 26 SEP 2007 HIGHEST RN 948239-70-1

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=> s benzodiazepine and dimethoxy and ethyl and methyl and dimethoxyphenyl

46059 BENZODIAZEPINE

849177 DIMETHOXY

8641602 ETHYL

13 ETHYLS

8641602 ETHYL

(ETHYL OR ETHYLS)

19398317 METHYL

97 METHYLS

19398317 METHYL

(METHYL OR METHYLS)

392011 DIMETHOXYPHENYL

L1 135 BENZODIAZEPINE AND DIMETHOXY AND ETHYL AND METHYL AND DIMETHOXYPHENYL

=> s l1 and 5H

530627 5H

L2 71 L1 AND 5H

=> s l2 and 4-methyl

20158339 4

19398317 METHYL

97 METHYLS

19398317 METHYL

(METHYL OR METHYLS)

2022956 4-METHYL

(4(W)METHYL)

L3 57 L2 AND 4-METHYL

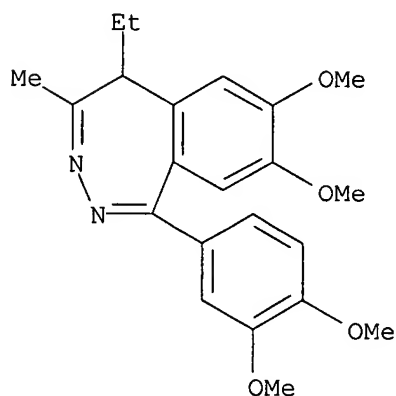
=> s l3 and 2-ethyl

24020984 2

8641602 ETHYL
13 ETHYLS
8641602 ETHYL
(ETHYL OR ETHYLS)
333214 2-ETHYL
(2(W)ETHYL)
L4 0 L3 AND 2-ETHYL

=> d 13 1-57

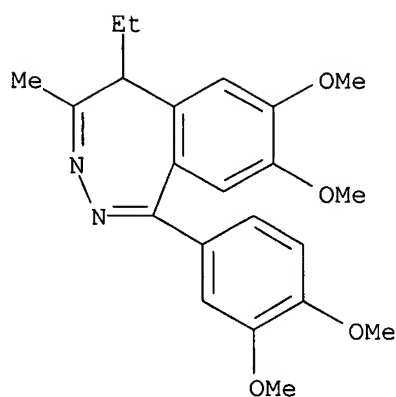
L3 ANSWER 1 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-51-8 REGISTRY
ED Entered STN: 29 Nov 2006
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
4-methyl-, (1R,5S)- (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

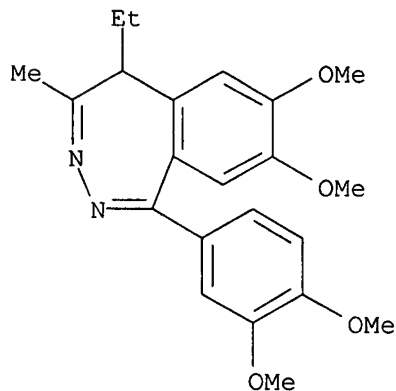
L3 ANSWER 2 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-50-7 REGISTRY
ED Entered STN: 29 Nov 2006
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
4-methyl-, (1S,5S)- (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

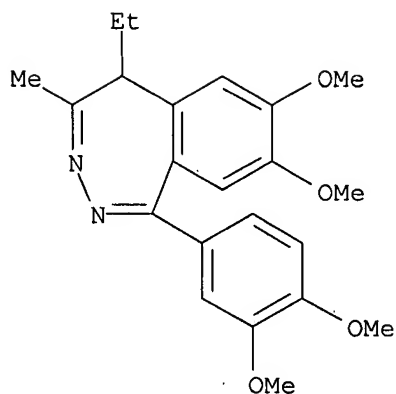
L3 ANSWER 3 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-49-4 REGISTRY
ED Entered STN: 29 Nov 2006
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (1R,5R)- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

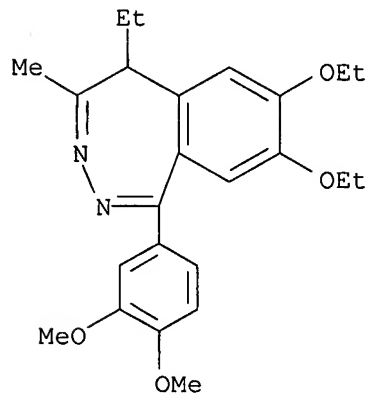
L3 ANSWER 4 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-48-3 REGISTRY
ED Entered STN: 29 Nov 2006
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (1S,5R)- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 5 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-28-3 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-** (CA INDEX NAME)
MF C24 H30 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 6 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-21-6 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine-7,8-diol, 1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-, (5S)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H22 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

L3 ANSWER 57 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 22345-47-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

OTHER NAMES:

CN 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine

CN 7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5H-2,3-benzodiazepine

CN EGYT 341

CN Grandaxin

CN Seriel

CN Tofisopam

DR 87555-18-8

MF C22 H26 N2 O4

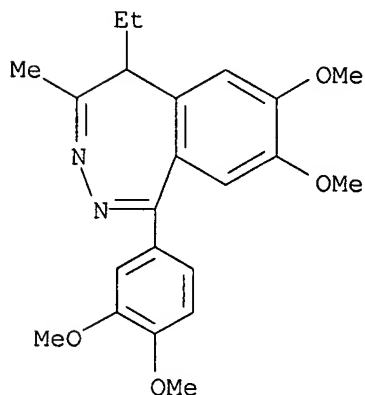
CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

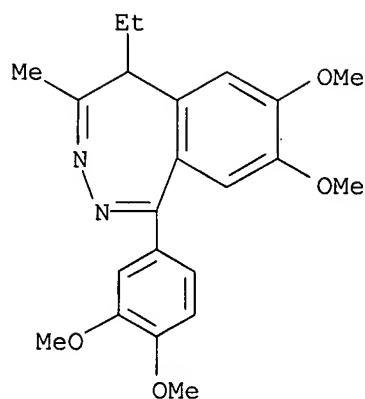


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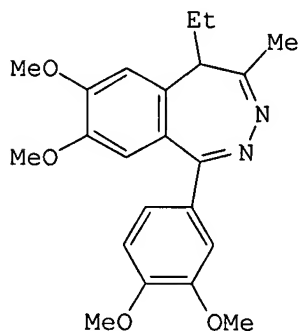
211 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

211 REFERENCES IN FILE CAPLUS (1907 TO DATE)



L7 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 1981:473687 CAPLUS
 DOCUMENT NUMBER: 95:73687
 TITLE: Pharmacological studies of **tofisopam**. 2
 AUTHOR(S): Ito, Chihiro; Shibutani, Yasunori; Suzuki, Kazuo;
 Yamaguchi, Kazuo; Noguchi, Katsuhiko; Yamazaki,
 Yoshio; Ohnishi, Haruo
 CORPORATE SOURCE: Res. Lab. Pharmacol., Mochida Pharm. Co. Ltd., Tokyo,
 Japan
 SOURCE: Iyakuhin Kenkyu (1981), 12(2), 587-600
 CODEN: IYKEDH; ISSN: 0287-0894
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 GI

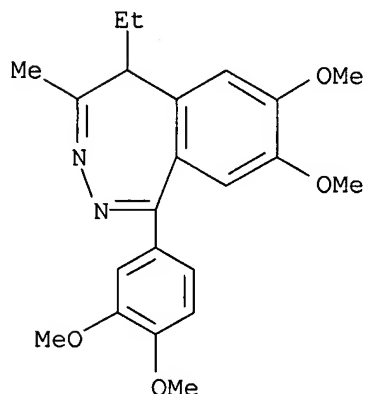


I.

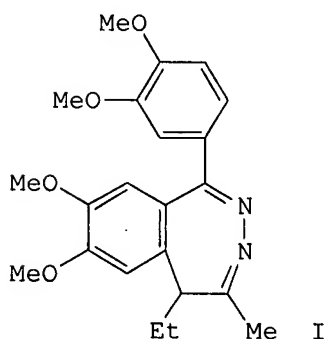
AB The pharmacol. effects of **tofisopam** (I) [22345-47-7]
 were studied in vivo and in vitro. Spontaneous locomotion and acetic
 acid-induced stretching were inhibited, **body temp.** was
 decreased, and pain threshold was elevated by oral I; these effects were
 similar to but lower in potency than those of diazepam. I.v. I was
 hypotensive in rabbits. I induced vasodilation in vitro. The drug
 inhibited adrenaline-induced arrhythmia and vasopressin-induced angina
 pectoris. At high concns., I relaxed isolated smooth muscle organs. I
 had no surface or infiltrative anesthetic activity, and had no effect on
 the neuromuscular junction, erythrocyte membrane, paw edema formation,
 vascular permeability, blood sugar level, or coagulation system.

IT 22345-47-7
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (pharmacol. of)

RN 22345-47-7 CAPLUS
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 1984:412141 CAPLUS
 DOCUMENT NUMBER: 101:12141
 TITLE: Production of microcapsules containing **tofisopam**
 AUTHOR(S): Devay, Attila; Racz, Istvan
 CORPORATE SOURCE: Semmelweis Orvostud. Egy. Gyogyszereszeti Intez., Budapest, 1092, Hung.
 SOURCE: Acta Pharmaceutica Hungarica (1984), 54(2), 84-9
 CODEN: APHGAO; ISSN: 0001-6659
 DOCUMENT TYPE: Journal
 LANGUAGE: Hungarian
 GI

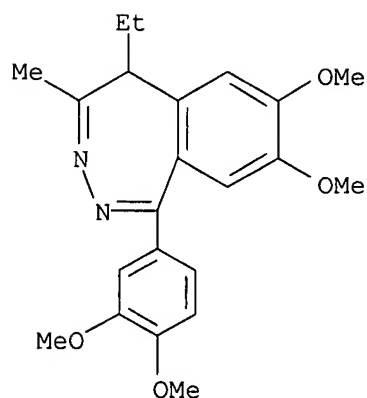


AB **Tofisopam** (I) [22345-47-7] was microencapsulated by melt dispersion, using cetyl alc. and Et cellulose as matrix materials. The particle size (x0) and homogeneity factor (n) of the capsules depended on the preparation **temp.**, mixing rate, mixing time, and ratio between the internal and external phase of the disperse system. The x0 decreased with **temp.**, in the 65-90° range, and with an increase in mixing rate. The n was maximum at 80°.

IT **22345-47-7**
 RL: PROC (Process)
 (microencapsulation of)

RN 22345-47-7 CAPLUS
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-

methyl- (CA INDEX NAME)



L7 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:709076 CAPLUS

DOCUMENT NUMBER: 121:309076

TITLE: A new method of studying **temperature** dependence and the effect of mobile phase composition on the retention mechanism in reversed phase liquid chromatography

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Laboratoire de Chimie Analytique, UFR des Sciences Medicales et Pharmaceutiques, Besancon, 25030, Fr.

SOURCE: Journal of Liquid Chromatography (1994), 17(13), 2809-20

CODEN: JLCHD8; ISSN: 0148-3919

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A rapid procedure is used to examine the effect of **temp.** and eluent composition on thermodyn. properties in high performance liquid chromatog.

is presented. The use of an exptl. design is proposed to study thermodyn. solution property trends for 10 benzodiazepines. Enthalpies and entropies of transfer (mobile to stationary phase) are calculated by evaluation of Van't Hoff plots. Enthalpies of transfer are neg for all cases examined. These data show that the entropy contribution to retention becomes more significant as solvent polarity decreases. The enthalpy-entropy compensation behavior is tested for varying mobile phase composition

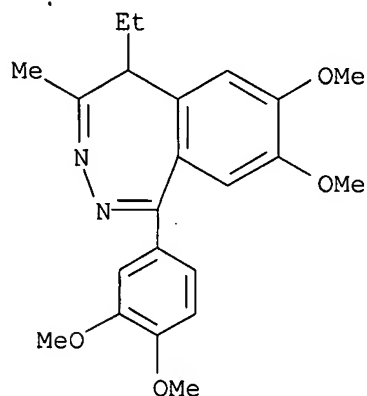
IT 22345-47-7, **Tofisopam**

RL: ANT (Analyte); ANST (Analytical study)

(eluent composition and **temp.** effects on retention mechanism in reversed phase liquid chromatog. and enthalpy-entropy compensation)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:472492 CAPLUS

DOCUMENT NUMBER: 139:53044

TITLE: Process for the preparation of **tofisopam** and new intermediates

INVENTOR(S): Molnarne Samu, Erika; Simig, Gyula; Vago, Pal; Greff, Zoltan

PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

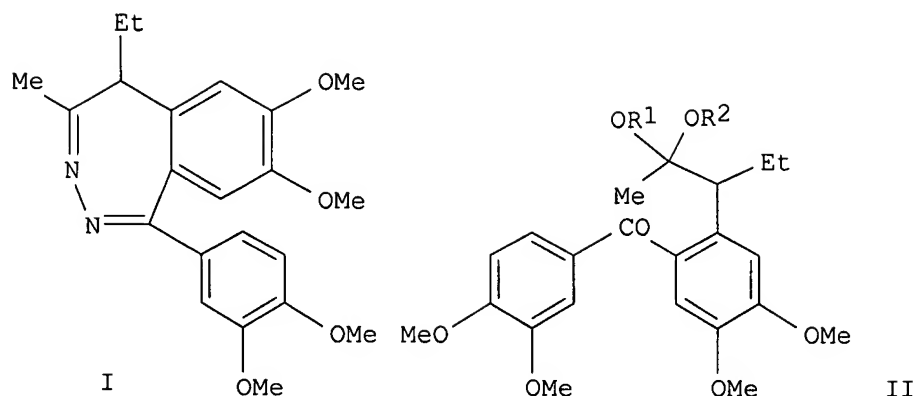
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003050092	A2	20030619	WO 2002-HU141	20021212
WO 2003050092	A3	20031106		
W:				
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW:				
GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
HU 200105326	A2	20030929	HU 2001-5326	20011213
HU 200105326	A3	20051128		
HU 225411	B1	20061128		
HU 200105327	A2	20030929	HU 2001-5327	20011213
HU 200105327	A3	20051128		
AU 2002348942	A1	20030623	AU 2002-348942	20021212
EP 1465879	A2	20041013	EP 2002-781451	20021212
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BG 108801	A	20050430	BG 2004-108801	20040713
PRIORITY APPLN. INFO.:			HU 2001-5326	A 20011213
			HU 2001-5327	A 20011213
			WO 2002-HU141	W 20021212
OTHER SOURCE(S):			CASREACT 139:53044; MARPAT 139:53044	
GI				



AB The invention relates to a new process for the preparation of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (I) that comprises reacting II (R1 and R2 independently each stands for C1-4-alkyl or together form C2-6-alkylene) with hydrazine or a hydrate or salt thereof formed with an inorg. or organic acid. I is a known anxiolytic agent. The invention also relates to new intermediates and a process for the preparation thereof. For example, I was prepared (84%) from II (R1OCOR2 = COCH2CH2O): to a mixture of 150 mmol of 99% HOAc and 90 mmol of 37% aqueous HCl, 30 mmol of II and 20 mL of MeOH were added; the mixture

was stirred under boiling for 20 min, whereupon 120 mmol of 98% hydrazine monohydrate was added in several portions; the reaction mixture was subjected to post-reaction at this temp. for 30 min, made alkaline, cooled and the precipitated product was filtered and dried. II (R1OCOR2 = COCH2CH2O) was prepared (65%) from 0.05 mol 3-(2-bromo-4,5-dimethoxyphenyl)pentan-2-one ethylene ketal (III) in 173 mL of THF cooled to -78° to which was added 0.06 mol BuLi as a 2.5 M hexane solution followed by 0.125 mol 3,4-dimethoxybenzaldehyde. III was prepared (92%) from 0.11 mol 3-(2-bromo-4,5-dimethoxyphenyl)pentan-2-one (IV) in 250 mL of toluene to which was added 0.20 mol ethylene glycol and 1.5 g of p-toluenesulfonic acid. IV was prepared (85%) from 0.50 mol 3-(3,4-dimethoxyphenyl)pentan-2-one in 500 mL of EtOH to which was added 0.52 mol N-bromosuccinimide. The drawback of known procedures resides in the fact that the precursor 1-phenyl-2-benzopyrilium salts and the benzoylphenylacetone derivative can be prepared only with low yields in

numerous

reaction steps. A further disadvantage of the known procedures is that during the synthesis Cr salts being extremely detrimental to the environment are formed.

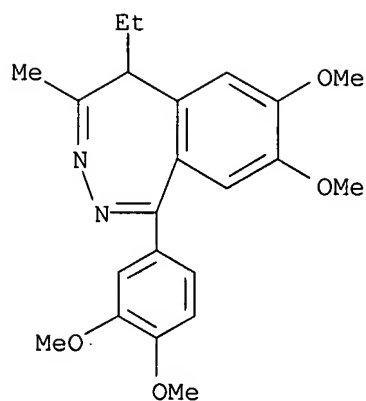
IT **22345-47-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine

RL: SPN (Synthetic preparation); PREP (Preparation)

(process for preparation of **tofisopam** and new intermediates)

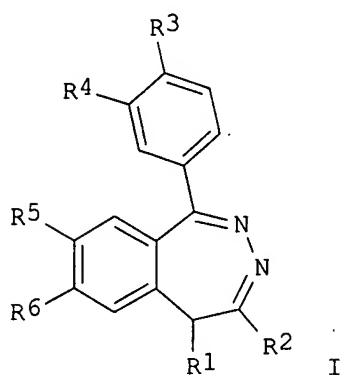
RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2004:1080692 CAPLUS
 DOCUMENT NUMBER: 142:56375
 TITLE: Modulation of dopamine responses with substituted (S)-2,3-benzodiazepines
 INVENTOR(S): Leventer, Steven M.; Harris, Herbert W.; Kucharik, Robert F.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 33 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004254173	A1	20041216	US 2003-461290	20030613
PRIORITY APPLN. INFO.:			US 2003-461290	20030613
OTHER SOURCE(S):	MARPAT 142:56375			
GI				



AB There is provided a method of modulating dopamine responses in the central nervous system of an individual or a method of treating a dopamine-mediated disorder in an individual not suffering from seizures or convulsions which comprises administering to the individual an effective amount of at least one compound of formula (I) [R1 = C1-7 hydrocarbyl or C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; wherein R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3, R4, R5, R6 = OH, C1-7 hydrocarbyl, CF3, C1-7 hydrocarbyloxy, acyloxy, NH2,

-NH(C1-6alkyl), -N(C1-6 alkyl)2, -NH-acyl, halogen; wherein R5 and R6 may combine to form a 5-, 6- or 7-membered heterocyclic ring] or pharmaceutically acceptable salts thereof or said compound comprising an (S)-enantiomer substantially free of the (R)-enantiomer of the same compound. The above dopamine-mediated disorder comprises a neurol. disorder or a neuropsychiatric disorder. The neurol. disorder includes Huntington's chorea, Parkinson's disease, periodic limb movement syndrome, restless leg syndrome, hyperkinesias, Tourette's syndrome, Pick's disease, punch drunk syndrome, progressive subnuclear palsy, multiple systems atrophy, Landau-Kleffner syndrome, benign essential blepharospasm, amyotrophic lateral sclerosis, medication-induced movement disorders, and cognitive disorders. The neuropsychiatric disorder includes psychosis, personality disorders, psychiatric mood disorders, conduct and impulse disorders, schizophrenia, bipolar disorders, dysphoric mania, anxiety disorders, depression, panic disorders, agoraphobia, obsessive-compulsive disorders and eating disorders. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride was dissolved in methanol (35 mL) at a temp. of 40°. After cooling to 20-25°, hydrazine hydrate (0.75 g, 15 mmol, dissolved in 5 mL methanol) was added and the resulting mixture was allowed to react while monitoring the reaction by HPLC and when complete, was evaporated to dryness. The residue was triturated with cold water (3 mL), filtered and dried to yield the crude 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**) which was subsequently triturated with hot EtOAc to yield the pure product. Racemic **tofisopam** was resolved by a Chirobiotic V column (ASTEAC, Whippany, N.J.) to give (R)-**tofisopam** and (S)-**tofisopam**. (R)-**tofisopam** did not affect apomorphine-induced hypothermia in mice. Racemic **tofisopam** at 64 mg/kg tended to behave as a weak dopamine antagonist, i.e., lowering the rectal temp. at the thirty and sixty minute time points. However this trend was not statistically significant. (S)-**tofisopam** behaved as a weak dopamine antagonist at the 16 mg/kg dose at sixty minutes after apomorphine administration, i.e., showing a slight but statistically significant elevation in temp. At the higher doses, (S)-**tofisopam** demonstrated dopamine antagonism at both the thirty minute and sixty minute time points, i.e., lowering the rectal temp. at both time points.

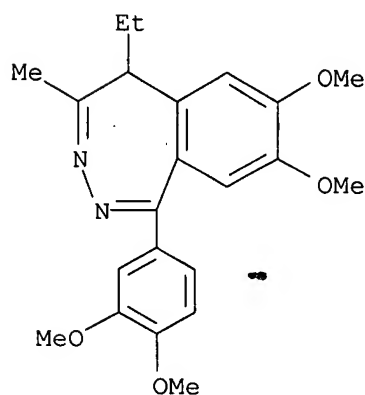
IT 22345-47-7P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:68450 CAPLUS

DOCUMENT NUMBER: 120:68450

TITLE: Optimizing mobile phase composition, its flow rate and column **temperature** in HPLC using an experimental design assisted with a simplex method

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Lab. Chim. Anal., UFR Sci. Med. Pharm., Besancon, Fr.

SOURCE: Journal of Liquid Chromatography (1993), 16(16), 3457-70

CODEN: JLCHD8; ISSN: 0148-3919

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A rapid procedure to sep. 10 benzodiazepines in HPLC is presented. The use of a modified G. E. P. Box and D. W. Behnken (1951, 1960, 1978) exptl. design assisted by a simplex method is proposed to sep. these compds. with only 13 chromatog. analyses to select the mobile phase composition, its flow rate and the column **temp.**. A flow rate of 0.77 mL/min with a percentage of MeOH of 49.95% in the mixture MeOH-H₂O and a column **temp.** of 51.62° gave the most efficient separation conditions.

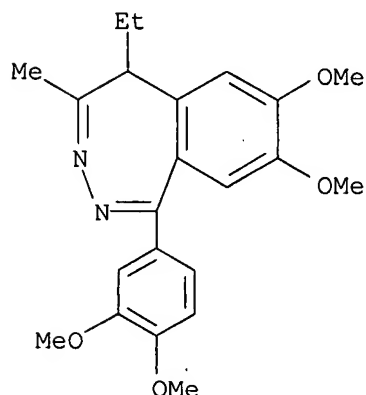
IT 22345-47-7, Tofisopam

RL: ANST (Analytical study); PROC (Process)

(separation of, from benzodiazepines by HPLC and chemometrics involving simplex optimization)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:449789 CAPLUS

DOCUMENT NUMBER: 123:198216

TITLE: Thermodynamic behavior of mixed benzodiazepines by a new liquid chromatographic method

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Lab. Chim. Analytique, Fac. Sci. Med. Pharm., Besancon, 25030, Fr.

SOURCE: Chromatographia (1995), 40(3/4), 193-6

CODEN: CHRGB7; ISSN: 0009-5893

PUBLISHER: Vieweg

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Using a rapid chemometric methodol. to determine the separation factor, α , at different **temps.**, Gibbs helmholtz parameters ($\Delta(\Delta H)$, $\Delta(\Delta S)$, $\Delta(\Delta G)$) of two adjacent benzodiazepines on a chromatogram were obtained from $\ln \alpha$ vs. T^{-1} plots. A **temp**

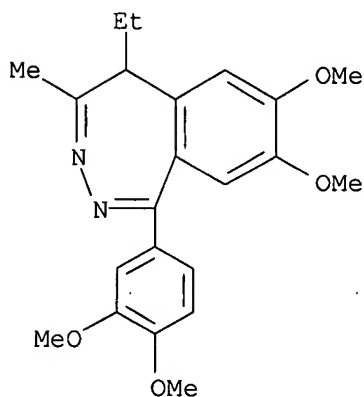
. dependent reversal of the elution order was studied and the mobile phase composition and column **temp.** were optimized to obtain the best separation. A flow rate of 0.80 mL. min⁻¹ with 52.6% methanol in the methanol-water mixture and a column **temp.** of 48°C gave the most efficient separation of ten benzodiazepines.

IT **22345-47-7, Tofisopam**

RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(thermodn. of mixed benzodiazepines by liquid chromatog.)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:425036 CAPLUS

DOCUMENT NUMBER: 131:204699

TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase

AUTHOR(S): Cahours, X.; Morin, Ph.; Dreux, M.

CORPORATE SOURCE: B.P. 6759, UPRES-A 6005, CNRS, Institut de Chimie Organique et Analytique, Orleans, 45 067, Fr.

SOURCE: Journal of Chromatography, A (1999), 845(1 + 2), 203-216

CODEN: JCRAEY; ISSN: 0021-9673

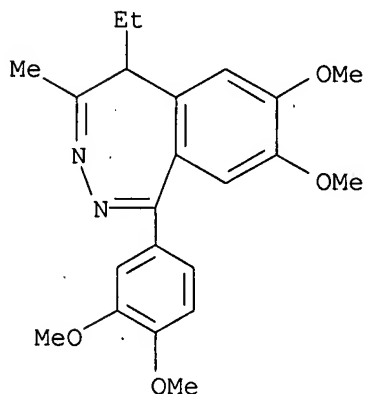
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effect of 3 physicochem. parameters (**temp.**, ionic strength and organic modifier content of the hydroorg. buffer) upon electrophoretic (electroosmotic flow, EOF, chromatog. retention factor and separation (retention time and peak efficiency)) performances was carefully investigated in capillary electrochromatog. (CEC) on a Ph bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, and **tofisopam**) were selected as test solutes. From the CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temp.** of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temp.** in CEC can mainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior. At last, the CEC separation of these benzodiazepines was achieved in 18 min, using Tris (pH 8)-MeCN (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 µm phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theor.

plates/m) and resolns. of 1.5 were easily obtained.
 IT **22345-47-7, Tofisopam**
 RL: ANT (Analyte); ANST (Analytical study)
 (ionic strength and modifier effect on capillary electrochromatog. of
 drugs on Ph silica stationary phase)
 RN 22345-47-7 CAPLUS
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-
 methyl- (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:805194 CAPLUS

DOCUMENT NUMBER: 123:358104

TITLE: Marked differences between acetonitrile/water and
 methanol/water mobile phase systems on the
 thermodynamic behavior of benzodiazepines in reversed
 phase liquid chromatography

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Lab. Chimie Analytique, Fac. Sciences Medicales
 Pharmaceutiques, Besancon, 25030, Fr.

SOURCE: Chromatographia (1995), 41(1/2), 84-7
 CODEN: CHRGB7; ISSN: 0009-5893

PUBLISHER: Vieweg

DOCUMENT TYPE: Journal

LANGUAGE: English

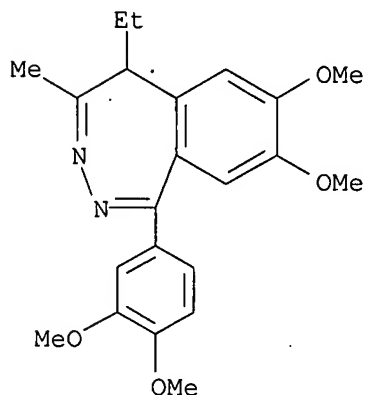
AB Two different methods were used to determine the separation factor α at
 different **temps.** and the Gibbs-Helmholtz parameters
 $(\Delta(\Delta H), \Delta(\Delta S))$ of two adjacent benzodiazepines on a
 chromatogram were obtained from plots of $\ln \alpha$ vs. $1/T$. The authors
 1st studied each factor (fraction of water ϕ in the ACN/water mixture
 and column **temp.** T), which controls the retention mechanism, and
 then the authors examined the simultaneous variation of all these factors.
 The changes in $\Delta(\Delta H)$ and $\Delta(\Delta S)$ in relation to a
 volume fraction of water ϕ in an ACN/water mixture were examined In the
 ACN/water system, $\Delta(\Delta H)$ was fairly constant in the acetonitrile
 region of $\phi \leq 0.52$ and appears to be a roughly linear function
 of ϕ for $\phi \geq 0.52$. In this system $\Delta(\Delta S)$ is
 approx. a parabolic function of ϕ with an optimum at $\phi \approx$
 0.52. The retention mechanism of ten benzodiazepines is significantly
 different in the methanol/water and ACN/water mixts. The separation
 optimization of these ten benzodiazepines was then considered. A fraction
 of water of 0.43 in the ACN/water mixture and a column **temp.** of
 44°C gave the most efficient separation conditions in the ACN/water
 mixture

IT **22345-47-7, Tofisopam**

RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(marked differences between acetonitrile/water and methanol/water
mobile phase systems on thermodyn. behavior of benzodiazepines in
reversed phase LC)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-
methyl- (CA INDEX NAME)



L7 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:669275 CAPLUS

DOCUMENT NUMBER: 136:47693

TITLE: Chiral supercritical fluid chromatography on porous
graphitic carbon using commercial dimethyl
 β -cyclodextrins as mobile phase additive

AUTHOR(S): Salvador, A.; Herbreteau, B.; Dreux, M.; Karlsson, A.;
Gyllenhaal, O.

CORPORATE SOURCE: Universite d'Orleans, UPRES A CNRS 6005, Institut de
Chimie Organique et Analytique, Orleans, F-45067, Fr.

SOURCE: Journal of Chromatography, A (2001), 929(1-2), 101-112
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Using dimethylated- β -cyclodextrin mixts. (MeCD) as chiral selectors
in CO₂-polar modifier mobile phase and porous graphitic carbon as
solid-phase, chiral supercrit. (or subcrit.) fluid chromatog. was
performed. The adsorbed quantity of MeCD onto the porous graphitic carbon
(Hypercarb) was measured for various chiral selector concns. using the
breakthrough method with evaporative light scattering detector. The
effects of MeCD concentration in the mobile phase, the nature of the polar
modifier, the outlet pressure, the column temp. and the nature
of the com. MeCD mixture on the retention and the enantioselectivities were
studied. For a given solute, the enantioselectivity is greatly dependent
on the com. MeCD mixture used. The retention mechanism was also studied.
The dominant mechanism for the chiral discrimination is the
diastereoisomeric complexation in the mobile phase.

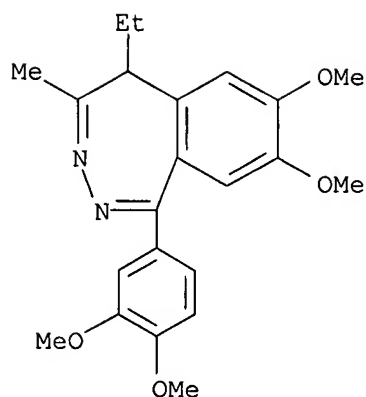
IT 22345-47-7, Tofisopam

RL: ANT (Analyte); PEP (Physical, engineering or chemical process); ANST
(Analytical study); PROC (Process)

(analyte; chiral supercrit. fluid chromatog. on porous graphitic carbon
using com. di-Me β -cyclodextrins as mobile phase additive)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-
methyl- (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:314905 CAPLUS

DOCUMENT NUMBER: 120:314905

TITLE: Study and optimization of column efficiency in HPLC: comparison of two methods for separating ten benzodiazepines

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Lab. Chim. Anal., UFR Sci. Med. Pharm., Besancon, Fr.

SOURCE: Journal of Liquid Chromatography (1994), 17(7), 1443-59

CODEN: JLCHD8; ISSN: 0148-3919

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To understand the influence of mobile phase composition, its flow rate and column temp. involved in high performance Liquid Chromatog., an exptl. design was used. The observed responses were the theor. plate number, the linear velocity of the mobile phase and a new chromatog. resolution function which provided the most efficient separation of 10 compds. as 10 benzodiazepines. Optimum conditions obtained were compared with another optimization method.

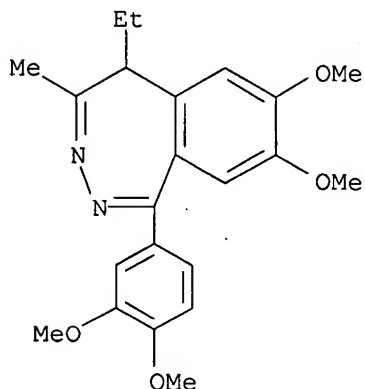
IT 22345-47-7, Tofisopam

RL: ANST (Analytical study)

(separation of, from benzodiazepines by HPLC, optimization of column efficiency in)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:347589 CAPLUS

DOCUMENT NUMBER: 126:321141

TITLE: A new approach to study benzodiazepine separation and the differences between a methanol/water and acetonitrile/water mixture on column efficiency in liquid chromatography

AUTHOR(S): Guillaume, Y.; Cavalli, E. J.; Peyrin, E.; Guinchard, C.

CORPORATE SOURCE: Laboratoire de Chimie Analytique, Faculte de Medecine Pharmacie, Besacon, 25030, Fr.

SOURCE: Journal of Liquid Chromatography & Related Technologies (1997), 20(11), 1741-1756
CODEN: JLCTFC; ISSN: 1082-6076

PUBLISHER: Dekker

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A chemometric methodol. was used to study column efficiency and the separation of 10 benzodiazepines in reversed phase liquid chromatog. New simple math. models and the organic modifier (OM) organization of ACN in the water, explained differences on column efficiency observed when ACN is chosen instead of CH₃OH. A new response function, which takes into account the separation quality and the anal. time, was proposed for the separation optimization.

The result, a mobile phase ACN/water (60/40) (V/V), with a flow rate = 1.00 mL/min and a column temp. = 47°C were optimum values for a rapid chromatog. separation

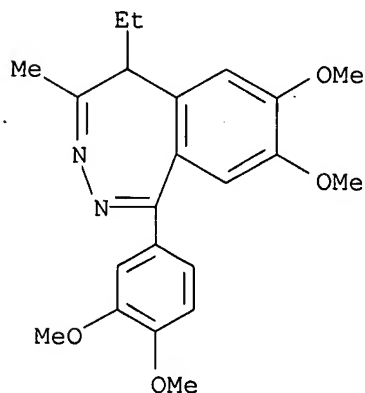
IT 22345-47-7, Tofisopam

RL: ANT (Analyte); ANST (Analytical study)

(separation of benzodiazepines by reversed-phase HPLC)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:455986 CAPLUS

DOCUMENT NUMBER: 125:157339

TITLE: Retention Mechanism of Weak Polar Solutes in Reversed Phase Liquid Chromatography

AUTHOR(S): Guillaume, Yves Claude; Guinchard, Christiane

CORPORATE SOURCE: Laboratoire de Chimie Analytique, Faculte de Medecine et Pharmacie, Besancon, 25030, Fr.

SOURCE: Analytical Chemistry (1996), 68(17), 2869-2873

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

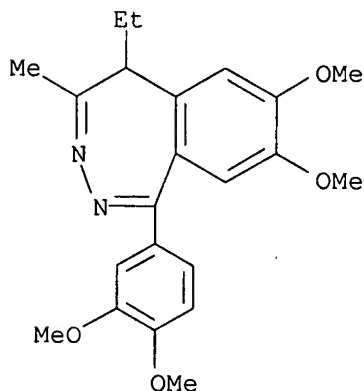
AB The retention mechanism of a weak polar solute, 10 benzodiazepines in reversed phase liquid chromatog., were studied over a wide range of mobile phase comps. The values of enthalpy (ΔH°) and entropy (ΔS°) of transfer from the mobile to the stationary phases were determined. The method studied each factor (water fraction Φ in the MeCN (ACN)/H₂O mixture and column temp.) controlling the retention mechanism. The changes in ΔH° and ΔS° as a function of the H₂O fraction Φ in the ACN/H₂O mixture were examined. These variations are explained using the organization of organic modifier (ACN) in clusters in the ACN/H₂O mixture. A change in the retention mechanism thus indicated when the ACN/H₂O mixture was used instead of the H-bonded mobile phase such as MeOH/H₂O. Enthalpy-entropy compensation revealed that the retention mechanism was independent of the H₂O fraction Φ but showed that differences between the mol. structures of the benzodiazepines contributed more significantly to changes in the retention process in the MeOH/H₂O mixture than in the ACN/H₂O mixture.

IT 22345-47-7, Tofisopam

RL: ANT (Analyte); PEP (Physical, engineering or chemical process); PRP (Properties); ANST (Analytical study); PROC (Process)
(retention mechanism of weak polar solutes in reversed phase liquid chromatog.)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1978:94763 CAPLUS

DOCUMENT NUMBER: 88:94763

TITLE: Rapid method for the determination of the heat occurring during the compression of pharmaceutical tablets

AUTHOR(S): Kovacs, B.; Toth, Z.; Baumann-Uderszky, Judit; Gyarmati, L.

CORPORATE SOURCE: Pharm. Inst., Semmelweis Med. Univ., Budapest, Hung.

SOURCE: Pharmazeutische Industrie (1977), 39(10), 1010-11

CODEN: PHINAN; ISSN: 0031-711X

DOCUMENT TYPE: Journal

LANGUAGE: German

AB A method for determining the amount of heat absorbed by tablets during compression

involves calorimetric measurement of the temp. rise of a known

amount of paraffin oil into which the freshly compressed tablets are poured.

The portable apparatus consists of measuring and reference systems, electrodes, and a digital readout device. The method can be used with tablets of varying weight and composition, produced under differing pressing conditions. The mean deviation in parallel detns. on various tablets was ≤5%.

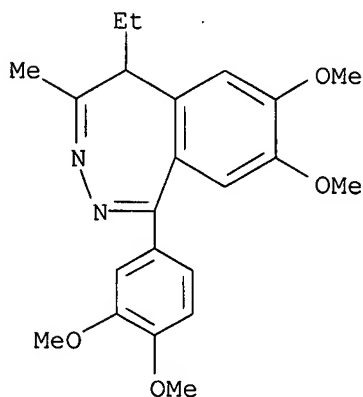
IT 22345-47-7

RL: BIOL (Biological study)

(tablets, heat of compression of, determination of)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1975:124585 CAPLUS

DOCUMENT NUMBER: 82:124585

TITLE: Heterocyclic compounds. II. 100-MHz PMR, pulse Fourier transform carbon-13 NMR, and mass spectroscopic studies of 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine

AUTHOR(S): Neszmelyi, Andras; Gacs-Baitz, Eszter; Horvath, Gyula; Lang, Tibor; Korosi, Jeno

CORPORATE SOURCE: Inst. Pharmacol. Res., Budapest, Hung.

SOURCE: Chemische Berichte (1974), 107(12), 3894-903
CODEN: CHBEAM; ISSN: 0009-2940

DOCUMENT TYPE: Journal

LANGUAGE: German

GI For diagram(s), see printed CA Issue.

AB NMR and mass spectroscopic studies on the diazepine (I) showed that the enamine 3-H-tautomer did not exist even at high temp. and that I had only 2 boat conformations in equilibrium with each other.

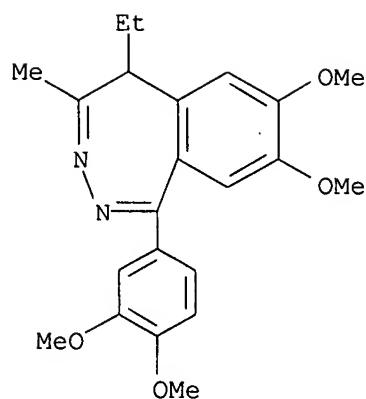
IT 22345-47-7

RL: PRP (Properties)

(conformation of, mass spectrum and NMR in relation to)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 22:31:56 ON 27 SEP 2007)

FILE 'REGISTRY' ENTERED AT 22:32:09 ON 27 SEP 2007

L1 135 S BENZODIAZEPINE AND DIMETHOXY AND ETHYL AND METHYL AND DIMETHO
 L2 71 S L1 AND 5H
 L3 57 S L2 AND 4-METHYL
 L4 0 S L3 AND 2-ETHYL

FILE 'CAPLUS' ENTERED AT 22:35:22 ON 27 SEP 2007

L5 226 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM
 E TEMPERATURE+ALL/CT
 L6 20 S L5 AND (TEMPERATURE OR BODY TEMPERATURE)
 L7 20 FOCUS L6 1-

=> s 15 and (hot flash or menopause)

452970 HOT

45 HOTS

453013 HOT

(HOT OR HOTS)

59984 FLASH

4389 FLASHES

62351 FLASH

(FLASH OR FLASHES)

872 HOT FLASH

(HOT (W) FLASH)

15149 MENOPAUSE

L8 3 L5 AND (HOT FLASH OR MENOPAUSE)

=> d ibib abs 1-3

L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:995773 CAPLUS

DOCUMENT NUMBER: 141:410971

TITLE: A preparation of 2,3-benzodiazepine derivatives,
 useful as antipyretic agents

INVENTOR(S): Harris, Herbert W.; Kucharik, Robert F.

PATENT ASSIGNEE(S): Vela Pharmaceuticals, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S.
 Ser. No. 369,823.

CODEN: USXXCO

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004162284	A1	20040819	US 2003-369823	20030219
US 2004224943	A1	20041111	US 2004-827839	20040419
PRIORITY APPLN. INFO.:			US 2003-369823	A2 20030219
			US 2004-781422	A2 20040217

OTHER SOURCE(S): MARPAT 141:410971
GI

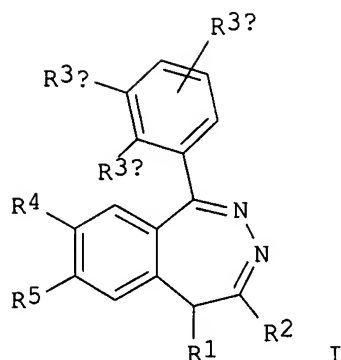
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of 2,3-benzodiazepine derivs. of formula I [wherein: R1 is hydrocarbyl or heteroalkyl; R2 is H or hydrocarbyl; R1 and R2 may combine to form a (carbo/hetero)cyclic ring; R3 and R4 are independently selected from OH, SH, NO2, halogen, or S-alkyl, etc.; R5 is substituted phenyl], useful as antipyretic agents. For instance, (S)-2,3-benzodiazepine derivative II was prepared via heterocyclization of diketone III with hydrazine and subsequent resolution. The prepared title compds. were tested in stress-induced hypothermia assay. (S)-enantiomer of **tofisopam** showed higher activity than the racemate or the (R)-enantiomer [dose: 64 mg/kg, (S)-**tofisopam**: 33 °C, (R)-**tofisopam**: 35.25 °C, racemate: 33.75 °C].

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 2004:964818 CAPLUS
 DOCUMENT NUMBER: 141:410972
 TITLE: Preparation of (R)-2,3-benzodiazepine derivatives and method of lowering body temperature with them
 INVENTOR(S): Leventer, Steven M.; Kucharik, Robert F.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 781,422.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224943	A1	20041111	US 2004-827839	20040419
US 2004162284	A1	20040819	US 2003-369823	20030219
US 2004229866	A1	20041118	US 2004-781422	20040217
PRIORITY APPLN. INFO.:			US 2003-369823	A2 20030219
			US 2004-781422	A2 20040217

OTHER SOURCE(S): MARPAT 141:410972
GI



AB An (R)-2,3-benzodiazepine of formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3a, R3b, R3c = H, -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halogen; provided at least one of R3a, R3b and R3c is other than H; R4, R5 = -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halo; or R4 and R5 may combine to form a 5-, 6- or 7-membered heterocyclic ring], substantially free from the corresponding (S)-enantiomer thereof with respect to the absolute conformation at the 5-position of the benzodiazepine ring, is administered to lower the body temperature of an individual. More specifically, the administered compound

is (R)-**tofisopam**, or a pharmaceutically-acceptable salt thereof and said individual is afflicted with a disorder associated with an elevated body temperature such as fever, malignant hyperthermia, serotonin syndrome, or **hot flashes** during **menopause** or perimenopause or occurred as side effects of drug therapy or subsequent to the removal of estrogen-producing tissue. Furthermore said individual is afflicted with a disorder such as cerebral ischemia or stroke wherein therapeutic benefit is achieved by lowering of the body temperature to a level below the normal body temperature. Thus, 4.41 g (10 mmol)

1-(3,4-dimethoxyphenyl)-3-methyl-

4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride was dissolved in methanol (35 mL) at 40°, cooled to 20-25°, treated with a solution of hydrazine hydrate (0.75 g, 15 mmol) in 5 mL methanol, and allowed to reaction. The reaction was monitored by HPLC and when complete, was evaporated to dryness. The residue is triturated with cold water (3 mL), filtered, and dried to yield crude (RS)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**). Racemic **tofisopam** was resolved by chiral chromatog. using a semipreparative Chirobiotic V column (ASTEC, Whippany, New Jersey) and Me tert-Bu ether/MeCN as the eluent to give (R)-**tofisopam** and (S)-**tofisopam**. In a stress induced hyperthermia assay using mice, racemic **tofisopam** demonstrated activity in lowering the core body temperature. (S)-**tofisopam** was more active than either the racemate or the (R)-enantiomer. However, the (R)-enantiomer showed greater tolerability compared with either the racemate or the (S)-enantiomer. For example, the mice treated with the (R)-enantiomer showed less sedation, abnormal gait, or ptosis, decreased muscle tone, decreased lacrimation, or decreased reactivity to touch compared with either (S)-enantiomer or the racemate.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:681397 CAPLUS

DOCUMENT NUMBER: 141:167829

TITLE: Method of lowering body temperature with (S)-

tofisopam
 INVENTOR(S): Harris, Herbert W.; Kucharik, Robert F.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 14 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004162284	A1	20040819	US 2003-369823	20030219
WO 2004073638	A2	20040902	WO 2004-US4726	20040217
WO 2004073638	A3	20050113		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004224943	A1	20041111	US 2004-827839	20040419
PRIORITY APPLN. INFO.:			US 2003-369823	A 20030219
			US 2004-781422	A2 20040217

AB (S)-**Tofisopam**, substantially isolated from the corresponding (R)-enantiomer of **tofisopam**, is administered to lower the body temperature of an individual.

=> file medline biosis embase
 COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
143.59	306.70

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
-17.94	-17.94

CA SUBSCRIBER PRICE

FILE 'MEDLINE' ENTERED AT 22:41:13 ON 27 SEP 2007

FILE 'BIOSIS' ENTERED AT 22:41:13 ON 27 SEP 2007

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FILE 'EMBASE' ENTERED AT 22:41:13 ON 27 SEP 2007

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=> s 22345-47-7/rn or egyt 341 or grandaxin or seriel or tofisopam
 'RN' IS NOT A VALID FIELD CODE
 'RN' IS NOT A VALID FIELD CODE
 'RN' IS NOT A VALID FIELD CODE

L9 481 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM

=> d his

(FILE 'HOME' ENTERED AT 22:31:56 ON 27 SEP 2007)

FILE 'REGISTRY' ENTERED AT 22:32:09 ON 27 SEP 2007

L1 135 S BENZODIAZEPINE AND DIMETHOXY AND ETHYL AND METHYL AND DIMETHO
L2 71 S L1 AND 5H
L3 57 S L2 AND 4-METHYL
L4 0 S L3 AND 2-ETHYL

FILE 'CAPLUS' ENTERED AT 22:35:22 ON 27 SEP 2007

L5 226 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM
E TEMPERATURE+ALL/CT
L6 20 S L5 AND (TEMPERATURE OR BODY TEMPERATURE)
L7 20 FOCUS L6 1-
E HOT FLASH+ALL/CT
E MENOPAUSE+ALL/CT
L8 3 S L5 AND (HOT FLASH OR MENOPAUSE)

FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 22:41:13 ON 27 SEP 2007

L9 481 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM

=> s l9 and (temperature or body temperature or hot flash or menopause or feeling hot or thermo?)

L10 22 L9 AND (TEMPERATURE OR BODY TEMPERATURE OR HOT FLASH OR MENOPAU
SE OR FEELING HOT OR THERMO?)

=> focu

PROCESSING COMPLETED FOR L10

L11 22 FOCUS L10 1-

=> d ibib abs 1-22

L11 ANSWER 1 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:196728 BIOSIS

DOCUMENT NUMBER: PREV200400197287

TITLE: Effects of S - **tofisopam** on physiological measurements in the ovariectomized rodent model of **menopause**.

AUTHOR(S): Harris, H. [Reprint Author]; Leventer, S. M. [Reprint Author]; Kucharik, R. [Reprint Author]; Gidner, J. [Reprint Author]; Speicher, B. [Reprint Author]; Keogh, J. C. [Reprint Author]; Galbraith, K. [Reprint Author]; Ye, N. [Reprint Author]; Sarnyai, Z.; Florino, L.; Klitenick, M.; Keim, K. L. [Reprint Author]

CORPORATE SOURCE: Vela Pharm, Lawrenceville, NJ, USA

SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 281.14.
<http://sfn.scholarone.com>. e-file.

Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 14 Apr 2004

Last Updated on STN: 14 Apr 2004

AB **Tofisopam** is a racemic, atypical, 2,3-benzodiazepine marketed in more than 15 countries outside of the United States. Although **tofisopam** was initially approved for use in anxiety disorders, the compound has since been found useful for the treatment of vasomotor and other symptoms associated with **menopause**. The identification of a chiral center in the molecule led to the purification of the two enantiomers of **tofisopam**, R-and S-**tofisopam**. The objective of the present study was to determine the effects of S-**tofisopam** on skin temperature in ovariectomized mice, a putative animal model of menopausal hot flashes. Female, ovariectomized 129SVEV (OVX) mice (Taconic, Germantown, NY) were received at 6 weeks of age. Consistent with the published literature on

ovariectomized animals, skin **temperature** measurements obtained over the course of 7 weeks following surgery indicated a steady rise that reached a maximum increase of approximately 2degreeC. Seven weeks after surgery, S-**tofisopam** was administered by intraperitoneal injection, producing a statistically significant drop in skin **temperature** 75 minutes after administration (1.35degreeC, p=0.001). Further behavioral and neuroendocrine studies employing OVX mice are underway. These findings are consistent with the published literature indicating that racemic **tofisopam** has clinical utility in treating vasomotor symptoms associated with **menopause**. In addition, these data indicate that S-**tofisopam** possesses the potential for clinical utility in the treatment of symptoms of **menopause** and possibly other disorders.

L11 ANSWER 2 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006429873 EMBASE
 TITLE: Method validation and determination of enantiomers and conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.
 AUTHOR: Hu M.; He P.; Chen Y.; Carr G.; Guo J.; Ye N.
 CORPORATE SOURCE: M. Hu, Patheon Inc., 2100 Syntex Court, Mississauga, Ont. L5N 7K9, Canada. mougang.hu@patheon.com
 SOURCE: Journal of Chromatography A, (29 Sep 2006) Vol. 1129, No. 1, pp. 47-53.
 Refs: 16
 ISSN: 0021-9673 CODEN: JCRAEY
 PUBLISHER IDENT.: S 0021-9673(06)01250-7
 COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 029 Clinical and Experimental Biochemistry
 037 Drug Literature Index
 039 Pharmacy
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 3 Oct 2006
 Last Updated on STN: 3 Oct 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 ± 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 µg/mL. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 °C, 25 °C, and 35 °C. .COPYRG. 2006 Elsevier B.V. All rights reserved.

L11 ANSWER 3 OF 22 MEDLINE on STN
 ACCESSION NUMBER: 2006537854 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 16844130
 TITLE: Method validation and determination of enantiomers and

conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.

AUTHOR: Hu Mougang; He Ping; Chen Yong; Carr Geoff; Guo Junan; Ye Naidong

CORPORATE SOURCE: Patheon Inc., Mississauga, Ont. L5N 7K9, Canada..
mougang.hu@patheon.com

SOURCE: Journal of chromatography. A, (2006 Sep 29) Vol. 1129, No. 1, pp. 47-53. Electronic Publication: 2006-07-17.
Journal code: 9318488. ISSN: 0021-9673.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200611

ENTRY DATE: Entered STN: 12 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 22 Nov 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 +/- 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 microg/mL. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 degrees C, 25 degrees C, and 35 degrees C.

L11 ANSWER 4 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2007:14827 BIOSIS

DOCUMENT NUMBER: PREV200700015228

TITLE: Method validation and determination of enantiomers and conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.

AUTHOR(S): Hu, Mougang; He, Ping; Chen, Yong; Carr, Geoff; Guo, Junan [Reprint Author]; Ye, Naidong

CORPORATE SOURCE: Patheon Inc, 2100 Syntex Court, Mississauga, ON L5N 7K9, Canada
mougan.hu@patheon.com; junan.guo@patheon.com

SOURCE: Journal of Chromatography A, (SEP 29 2006) Vol. 1129, No. 1, pp. 47-53.
CODEN: JOCRAM. ISSN: 0021-9673.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 20 Dec 2006
Last Updated on STN: 20 Dec 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation

of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 +/- 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 $\mu\text{g/mL}$. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 degrees C, 25 degrees C, and 35 degrees C. (c) 2006 Elsevier B.V. All rights reserved.

L11 ANSWER 5 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1995252142 EMBASE
TITLE: Marked differences between acetonitrile/water and methanol/water mobile phase systems on the **thermodynamic** behavior of benzodiazepines in reversed phase liquid chromatography.
AUTHOR: Guillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratoire de Chimie Analytique, Fac. Sciences Medicales/Pharmaceut., Place St. Jacques, 25030 Besancon Cedex, France
SOURCE: Chromatographia, (1995) Vol. 41, No. 1-2, pp. 84-87. ISSN: 0009-5893 CODEN: CHRGB7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 1995
Last Updated on STN: 12 Sep 1995

AB Two different methods were used to determine the separation factor α at different **temperatures** and the Gibbs-Helmholtz parameters ($\Delta(\Delta H)$, $\Delta(\Delta S)$) of two adjacent benzodiazepines on a chromatogram were obtained from plots of $\ln \alpha$ versus $1/T$. We first studied each factor (fraction of water Φ in the ACN/water mixture and column **temperature** T), which controls the retention mechanism, and then we examined the simultaneous variation of all these factors. The changes in $\Delta(\Delta H)$ and $\Delta(\Delta S)$ in relation to a volume fraction of water Φ in an ACN/water mixture were examined. In the ACN/water system, $\Delta(H)$ was fairly constant in the acetonitrile region of Φ 0.52 and appears to be a roughly linear function of Φ for Φ 0.52. In this system $\Delta(\Delta S)$ is approximately a parabolic function of Φ with an optimum at Φ .simeq. 0.52. The retention mechanism of ten benzodiazepines was found to be significantly different in the methanol/water and ACN/water mixtures. The separation optimization of these ten benzodiazepines was then considered. A fraction of water of 0.43 in the ACN/water mixture and a column **temperature** of 44°C gave the most efficient separation conditions in the ACN/water mixture.

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ACCESSION NUMBER: 1983207312 EMBASE
TITLE: **Tofisopam**, a new 2,3-benzodiazepine. Inhibition of changes induced by stress loading and hypothalamic stimulation.
AUTHOR: Yamaguchi K.; Suzuki K.; Niho T.; et. al.

CORPORATE SOURCE: Fuji Cent. Res. Lab., Mochida Pharm. Co. Ltd., Gotemba,
Shizuoka 412, Japan
SOURCE: Canadian Journal of Physiology and Pharmacology, (1983)
Vol. 61, No. 6, pp. 619-625.
ISSN: 0008-4212 CODEN: CJPPA3
COUNTRY: Canada
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: French
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on the following gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and γ -oryzanol. **Tofisopam** (30 and 100 mg/kg, po) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, iv, or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temperature**, and mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. However, diazepam and γ -oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. From these results, it can be concluded that **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 7 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1977055898 EMBASE
TITLE: The treatment of climacteric syndrome with tofizopam (**Grandaxin**).
AUTHOR: Csillag M.; Gimes G.; Kiss C.; et. al.
CORPORATE SOURCE: I Dept. Gynaecol., Semmelweis Univ. Med. Sch., Budapest, Hungary
SOURCE: Therapia Hungarica, (1975) Vol. 23, No. 4, pp. 164-169.
ISSN: 0133-3909 CODEN: THHUAF
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
020 Gerontology and Geriatrics
030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English

AB 172 climacteric patients were treated with **Grandaxin**. According to the results of examinations **Grandaxin** proved to be of clinical value in the treatment of climacteric syndrome. In the majority of cases (with complaints of mild, resp. moderate intensity) it decreased or controlled the psychic and neurovegetative symptoms when given as single agent. The drug ameliorates the general condition of the patients by moderating the majority of complaints, and by increasing the tolerance

of symptoms as a consequence or by relieving them. The application of hormone therapy is indicated only in severe cases; in these cases **Grandaxin** prolongs the hormone effect and reduces the requirement for frequent hormone administration. The safety of **Grandaxin** treatment has to be emphasized. Its great advantage is that it does not influence or only beneficially influences the daily working ability of the patients.

L11 ANSWER 8 OF 22 MEDLINE on STN
ACCESSION NUMBER: 83284617 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6136319
TITLE: **Tofisopam**, a new 2,3-benzodiazepine.. Inhibition of changes induced by stress loading and hypothalamic stimulation.
AUTHOR: Yamaguchi K; Suzuki K; Niho T; Shimora M; Ito C; Ohnishi H
SOURCE: Canadian journal of physiology and pharmacology, (1983 Jun) Vol. 61, No. 6, pp. 619-25.
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198310
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 21 Oct 1983

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on the following: gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and gamma-oryzanol. **Tofisopam** (30 and 100 mg/kg, po) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, iv, or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe temperature, and mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. However, diazepam and gamma-oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. From these results, it can be concluded that **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 9 OF 22 MEDLINE on STN
ACCESSION NUMBER: 82118267 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7327446
TITLE: Effects of **tofisopam** on the physiological changes induced by stress loading and hypothalamic stimulation (author's transl).
AUTHOR: Ohnishi H; Ito C; Suzuki K; Niho T; Shimora M; Yamaguchi K
SOURCE: Nippon yakurigaku zasshi. Folia pharmacologica Japonica, (1981 Sep) Vol. 78, No. 3, pp. 139-44.
Journal code: 0420550. ISSN: 0015-5691.
Report No.: NASA-82118267.
PUB. COUNTRY: Japan

DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198204
ENTRY DATE: Entered STN: 17 Mar 1990
Last Updated on STN: 17 Mar 1990
Entered Medline: 12 Apr 1982

AB Effects of **tofisopam** on the gastric ulceration induced by immobilization stress in olfactory-bulbectomized rats, propulsion of the small intestine caused by water immersion-stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits were investigated. Immobilization stress loading of 16.5 hours each for 10 days caused the augmentation of incidence and average index of gastric ulceration in olfactory-bulbectomized rats, compared with non-treated rats. **Tofisopam** 100 mg/kg, p.o. significantly inhibited the gastric ulceration in olfactory-bulbectomized rats. Water immersion-stress loading for 2 hours caused a significant increase in propulsion of the small intestine in rats. This increase was reversed to control levels after the oral administration of **tofisopam** in a dose of 100 mg/kg. **Tofisopam** at dose of 1 mg/kg i.v. inhibited the contraction of ear microvessels, the decrease in earlobe **temperature** and the mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. Moreover, these inhibitions were also shown by the intra-cerebrospinal injection of **tofisopam** at a dose of 0.1 mg/kg. From these results, it is concluded that **tofisopam** could restore the autonomic abnormality induced by stress-loading and exerts such effects by acting on the hypothalamus, an area of the brain, which regulates autonomic nervous functions.

L11 ANSWER 10 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1984:181073 BIOSIS
DOCUMENT NUMBER: PREV198477014057; BA77:14057
TITLE: **TOFISOPAM** A NEW 2 3 BENZODIAZEPINE INHIBITION OF CHANGES INDUCED BY STRESS LOADING AND HYPOTHALAMIC STIMULATION.
AUTHOR(S): YUAMAGUCHI K [Reprint author]; SUZUKI K; NIHO T; SHIMORA M; ITO C; OHNISHI H
CORPORATE SOURCE: FUJI CENTRAL RESEARCH LABORATORY, MOCHIDA PHARMACEUTICAL CO, LTD, 722, JIMBA-AZA-UENOHARA, GOTEMBA, SHIZUOKA 412, JAPAN
SOURCE: Canadian Journal of Physiology and Pharmacology, (1983) Vol. 61, No. 6, pp. 619-625.
CODEN: CJPPA3. ISSN: 0008-4212.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and γ -oryzanol. **Tofisopam** (30 and 100 mg/kg, p.o. [orally]) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, i.v. or 0.1 mg/kg by

intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temperature** and mydriasis induced by electrical stimulation of the medial hypothalamus area in rabbits. Diazepam and γ -oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. **Tofisopam** evidently restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 11 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1982:225751 BIOSIS
DOCUMENT NUMBER: PREV198273085735; BA73:85735
TITLE: EFFECTS OF **TOFISOPAM** ON THE PHYSIOLOGICAL CHANGES INDUCED BY STRESS LOADING AND HYPOTHALAMIC STIMULATION.
AUTHOR(S): OHNISHI H [Reprint author]; ITO C; SUZUKI K; NIHO T; SHIMORA M; YAMAGUCHI K
CORPORATE SOURCE: RESEARCH LAB OF PHARMACOLOGY, MOCHIDA PHARMACEUTICAL CO LTD, KAMIYA 1-1-1, KITA-KU, TOKYO 115, JAPAN
SOURCE: Folia Pharmacologica Japonica, (1981) Vol. 78, No. 3, pp. 139-144.
CODEN: NYKZAU. ISSN: 0015-5691.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: JAPANESE

AB Effects of **tofisopam** on gastric ulceration induced by immobilization stress in olfactory-bulbectomized rats, propulsion of the small intestine caused by water immersion-stress in rats, and autonomic responses to electrical stimulation of the hypothalamus in rabbits were investigated. Immobilization stress loading of 16.5 h each for 10 days caused the augmentation of incidence and average index of gastric ulceration in olfactory-bulbectomized rats, compared with non-treated rats. **Tofisopam**, 100 mg/kg, orally, significantly inhibited the gastric ulceration in olfactory-bulbectomized rats. Water immersion-stress loading for 2 h caused a significant increase in propulsion of the small intestine in rats. This increase was reversed to control levels after the oral administration of 100 mg/kg **tofisopam**. **Tofisopam**, 1 mg/kg i.v., inhibited the contraction of ear microvessels, the decrease in earlobe **temperature** and the mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. These inhibitions were also shown by the intra-cerebrospinal injection of **tofisopam** at 0.1 mg/kg. Apparently, **tofisopam** could restore the autonomic abnormality induced by stress-loading, and exerts such effects by acting on the hypothalamus, which regulates autonomic nervous functions.

L11 ANSWER 12 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:334551 BIOSIS
DOCUMENT NUMBER: PREV199900334551
TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase.
AUTHOR(S): Cahours, X.; Morin, Ph. [Reprint author]; Dreux, M.
CORPORATE SOURCE: Institut de Chimie Organique et Analytique, CNRS UPRES-A 6005, 45 067, Orleans Cedex 2, France
SOURCE: Journal of Chromatography A, (June 11, 1999) Vol. 845, No. 1-2, pp. 203-216. print.
CODEN: JOCRAM. ISSN: 0021-9673.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 1999
Last Updated on STN: 24 Aug 1999

AB The influence of three physicochemical parameters (**temperature**,

ionic strength and organic modifier content of the hydro-organic buffer) upon electrophoretic (electroosmotic flow, EOF, chromatographic (retention factor) and separation (retention time, peak efficiency) performances has been carefully investigated in capillary electrochromatography (CEC) on a phenyl bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, **tofisopam**) have been selected as test solutes. From our CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temperature** of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temperature** in CEC can mainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior. At last, the CEC separation of these benzodiazepines has been achieved in 18 min. using TriscntdotHCl (pH 8)-acetonitrile (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 μ m phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theoretical plates/meter) and resolutions of 1.5 are easily obtained.

L11. ANSWER 13 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999234493 EMBASE
 TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase.
 AUTHOR: Cahours X.; Morin Ph.; Dreux M.
 CORPORATE SOURCE: Ph. Morin, Inst. Chimie Organique/Analytique, CNRS UPRES-A 6005, B.P. 6759, 45067 Orleans Cedex 2, France
 SOURCE: Journal of Chromatography A, (11 Jun 1999) Vol. 845, No. 1-2, pp. 203-216.
 Refs: 42
 ISSN: 0021-9673 CODEN: JCRAEY
 PUBLISHER IDENT.: S 0021-9673(99)00007-2
 COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
 FILE SEGMENT: 029 Clinical and Experimental Biochemistry
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Jul 1999
 Last Updated on STN: 27 Jul 1999

AB The influence of three physicochemical parameters (**temperature**, ionic strength and organic modifier content of the hydro-organic buffer) upon electrophoretic (electroosmotic flow, EOF, chromatographic (retention factor) and separation (retention time, peak efficiency) performances has been carefully investigated in capillary electrochromatography (CEC) on a phenyl bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, **tofisopam**) have been selected as test solutes. From our CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temperature** of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temperature** in CEC can mainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior. At last, the CEC separation of these benzodiazepines has been achieved in 18 min, using Tris.HCl (pH 8)-acetonitrile (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 μ m phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theoretical plates/meter) and resolutions of 1.5 are easily obtained. Copyright (C)

L11 ANSWER 14 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1993309732 EMBASE
TITLE: Optimizing mobile phase composition, its flow rate and column **temperature** in HPLC using an experimental design assisted with a simplex method.
AUTHOR: Guillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratoire de Chimie Analytique, UFR des Scis. Medicales/Pharmaceut., Place St. Jacques, Besancon, France
SOURCE: Journal of Liquid Chromatography, (1993) Vol. 16, No. 16, pp. 3457-3470.
Refs: 14
ISSN: 0148-3919 CODEN: JLCHD8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Nov 1993
Last Updated on STN: 21 Nov 1993

AB In this work, a rapid procedure to separate ten compounds in high performance liquid chromatography is presented. The use of an experimental design assisted with a simplex method is proposed to separate these compounds with only thirteen chromatographic analyses to select the mobile phase composition, its flow rate and the column **temperature**. A flow rate of 0.77 ml/min with a percentage of methanol of 49.95% in the mixture methanol-water and a column **temperature** of 51.62°C gave the most efficient separation conditions.

L11 ANSWER 15 OF 22 MEDLINE on STN
ACCESSION NUMBER: 93297300 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8517164
TITLE: [Additional data from the NMR investigation of tofizopam]. Adatok a tofizopam NMR spektroszkopiai vizsgalatahoz.
AUTHOR: Kovesdi I; Ujszaszy K
CORPORATE SOURCE: EGIS Gyogyszergyar Rt., Budapest.
SOURCE: Acta pharmaceutica Hungarica, (1993 Mar) Vol. 63, No. 2, pp. 53-6.
Journal code: 0414322. ISSN: 0001-6659.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Hungarian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 6 Aug 1993
Last Updated on STN: 6 Aug 1993
Entered Medline: 22 Jul 1993

AB The seven-membered ring of Tofizopam exists in two stable conformations in solutions. Separately detectable (Et)Me triplets of the conformers offered us a way for quantitative determination of conformer ratios. **Temperature** dependence of free enthalpy of conformers were calculated from the measured conformer ratios in different **temperatures**. Entropy component of the free enthalpy proved to be 35% of the whole at 36 degrees C. Half period of attaining equilibrium ratio of conformers was 2 hours at 36 degrees C.

L11 ANSWER 16 OF 22 MEDLINE on STN

ACCESSION NUMBER: 90272918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1971957
TITLE: Pharmacological validation of a novel animal model of anticipatory anxiety in mice.
AUTHOR: Lecci A; Borsini F; Volterra G; Meli A
CORPORATE SOURCE: A. Menarini Pharmaceuticals, Pharmacological Research Department, Firenze, Italy.
SOURCE: Psychopharmacology, (1990) Vol. 101, No. 2, pp. 255-61. Journal code: 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 10 Aug 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 12 Jul 1990

AB The current study investigates the action of anxiolytics, antidepressants, neuroleptics, antipyretics, muscle relaxants, antihypertensives and naloxone in a novel animal model of anxiety, based on the evidence that mice removed last from their cage develop hyperthermia (stress-induced hyperthermia, SIH) when compared to those removed first. Alprazolam (0.15-0.6 mg/kg), chlordiazepoxide (25 mg/kg), estazolam (1 mg/kg), phenobarbital (20 mg/kg), ethanol (2 and 4 g/kg), buspirone (5 and 10 mg/kg) and prazosin (1 and 2 mg/kg), as well as repeatedly administered diazepam (5 mg/kg), inhibited SIH. In contrast, **tofisopam** (12.5-200 mg/kg), desipramine (15 and 30 mg/kg), amitriptyline (10 mg/kg), fluoxetine (10 and 20 mg/kg), tranylcypromine (5 and 10 mg/kg), chlorpromazine (1 and 2 mg/kg), clozapine (2 and 4 mg/kg), pimozide (0.5 and 1 mg/kg), 1-sulpiride (15 and 30 mg/kg), 1-propranolol (5 and 10 mg/kg), acetyl salicylic acid (200 and 400 mg/kg), indomethacin (2.5 and 5 mg/kg), verapamil (2.5 and 5 mg/kg), captopril (25 and 50 mg/kg), dantrolene (10 and 20 mg/kg), mephenesin (300 and 600 mg/kg), d-amphetamine (1 and 4 mg/kg) and naloxone (2.5 and 15 mg/kg) were inactive, as were 10 mg/kg imipramine, amitriptyline and fluoxetine injected every day for 21 days. Reserpine at high doses (1.25 and 2.5 mg/kg) but not at a lower dose (0.62 mg/kg) prevented SIH, but in this case animals showed a behavioural syndrome which could have interfered with the occurrence of the hyperthermia.

L11 ANSWER 17 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1994131566 EMBASE
TITLE: Study and optimization of column efficiency in HPLC: Comparison of two methods for separating ten benzodiazepines.
AUTHOR: Gillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Gillaume, Laboratoire Chimie Analytique, UFR Sci. Medicales/Pharmaceutiques, Place St. Jacques, Besancon, France
SOURCE: Journal of Liquid Chromatography, (1994) Vol. 17, No. 7, pp. 1443-1459.
Refs: 17
ISSN: 0148-3919 CODEN: JLCHD8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jun 1994
Last Updated on STN: 2 Jun 1994

AB To understand the influence of mobile phase composition, its flow rate and column **temperature** involved in high performance Liquid Chromatography, an experimental design was used. The observed responses were the theoretical plate number, the linear velocity of the mobile phase and a new chromatographic resolution function which provided the most efficient separation of ten compounds as ten benzodiazepines. Optimum conditions obtained were compared with another optimization method.

L11 ANSWER 18 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1993125464 EMBASE
TITLE: Additional data to the NMR investigation of **tofisopam**.
AUTHOR: Kovesdi I.; Ujszaszy K.
CORPORATE SOURCE: I. Kovesdi, EGIS Gyogyszergyar Rt., Pf. 100, H-1475 Budapest 10, Hungary
SOURCE: Acta Pharmaceutica Hungarica, (1993) Vol. 63, No. 2, pp. 53-56.
ISSN: 0001-6659 CODEN: APHGAO
COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: Hungarian
SUMMARY LANGUAGE: English; Hungarian
ENTRY DATE: Entered STN: 6 Jun 1993
Last Updated on STN: 6 Jun 1993

L11 ANSWER 19 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001318058 EMBASE
TITLE: Chiral supercritical fluid chromatography on porous graphitic carbon using commercial dimethyl β -cyclodextrins as mobile phase additive.
AUTHOR: Salvador A.; Herbreteau B.; Dreux M.; Karlsson A.; Gyllenhaal O.
CORPORATE SOURCE: B. Herbreteau, Inst. de Chimie Organique/Analytique, UPRES A CNRS 6005, Universite d'Orleans, BP 6759, F-45067 Orleans Cedex 02, France. bernard.herbreteau@univ-orleans.fr
SOURCE: Journal of Chromatography A, (21 Sep 2001) Vol. 929, No. 1-2, pp. 101-112.
Refs: 62
ISSN: 0021-9673 CODEN: JCRAEY
PUBLISHER IDENT.: S 0021-9673(01)01155-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 2001
Last Updated on STN: 27 Sep 2001

AB Using dimethylated- β -cyclodextrin mixtures (MeCD) as chiral selectors in CO(2)-polar modifier mobile phase and porous graphitic carbon as solid-phase, chiral supercritical (or subcritical) fluid chromatography was performed. The adsorbed quantity of MeCD onto the porous graphitic carbon (Hypercarb) was measured for various chiral selector concentrations using the breakthrough method with evaporative light scattering detector. The effects of MeCD concentration in the mobile phase, the nature of the polar modifier, the outlet pressure, the column **temperature** and the nature of the commercial MeCD mixture on the retention and the enantioselectivities were studied. For a given solute, the enantioselectivity is greatly dependent on the commercial MeCD mixture used. The retention mechanism was also studied. From the data, we find

that the dominant mechanism for the chiral discrimination is the diastereoisomeric complexation in the mobile phase. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

L11 ANSWER 20 OF 22 MEDLINE on STN
ACCESSION NUMBER: 76246699 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7857
TITLE: The treatment of climacteric syndrome with tofizopam (**Grandaxin**).
AUTHOR: Csillag M; Gimes G; Kiss C; Sebo J; Toth F; Toth K; Bolla K
SOURCE: Therapia Hungarica (English edition), (1975) Vol. 23, No. 4, pp. 164-9.
Journal code: 8706535. ISSN: 0133-3909.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197609
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 25 Sep 1976

L11 ANSWER 21 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997163364 EMBASE
TITLE: A new approach to study benzodiazepine separation and the differences between a methanol/water and acetonitrile/water mixture on column efficiency in liquid chromatography.
AUTHOR: Guillaume Y.; Cavalli E.J.; Peyrin E.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratoire Chimie Analytique, Faculte de Medecine Pharmacie, Place Saint-Jacques 25030, Besancon Cedex, France
SOURCE: Journal of Liquid Chromatography and Related Technologies, (1997) Vol. 20, No. 11, pp. 1741-1756.
Refs: 25
ISSN: 1082-6076 CODEN: JLCTFC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Jun 1997
Last Updated on STN: 18 Jun 1997

AB A chemometric methodology was used to study column efficiency and the separation of 10 benzodiazepines in reversed phase liquid chromatography. New simple mathematical models and the organic modifier (OM) organization of ACN in the water, explained differences on column efficiency observed when ACN is chosen instead of CH(3)OH. A new response function, which takes into account the separation quality and the analysis time, was proposed for the separation optimization. The result, a mobile phase ACN/water (60/4) (V/V), with a flow rate = 1.00 mL/min and a column **temperature** = 47°C were optimum values for a rapid chromatographic separation.

L11 ANSWER 22 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2006264838 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16689340
TITLE: Climacteric disorders.
AUTHOR: Makita Kazuya; Horiguchi Fumi; Aoki Daisuke
CORPORATE SOURCE: Department of Obstetrics and Gynecology, School of Medicine, Keio University.

SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2006
Apr) Vol. 64 Suppl 4, pp. 394-9. Ref: 14
Journal code: 0420546. ISSN: 0047-1852.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

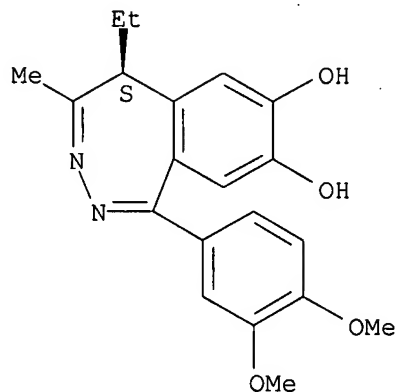
LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200606

ENTRY DATE: Entered STN: 13 May 2006
Last Updated on STN: 1 Jul 2006
Entered Medline: 30 Jun 2006

Absolute stereochemistry.

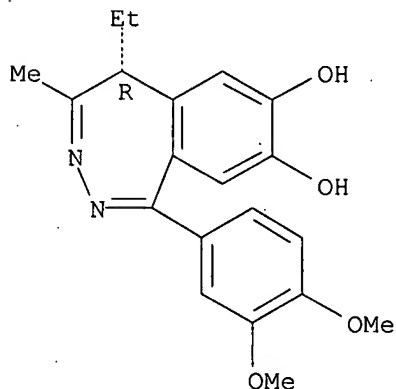


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 7 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-20-5 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine-7,8-diol, 1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-, (5R)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H22 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



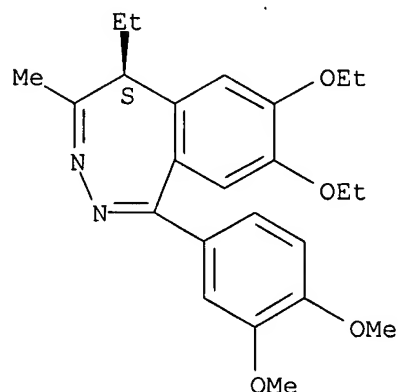
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 8 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-03-4 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-, (5S)-** (CA INDEX NAME)
FS STEREOSEARCH

MF C24 H30 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

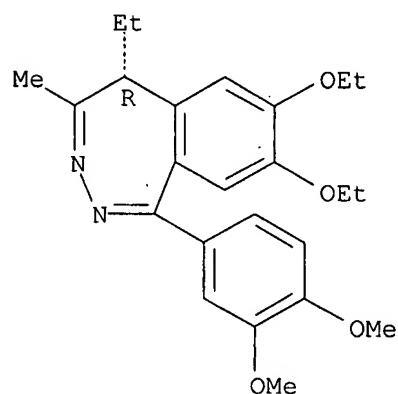


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 9 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-02-3 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-, (5R)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H30 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

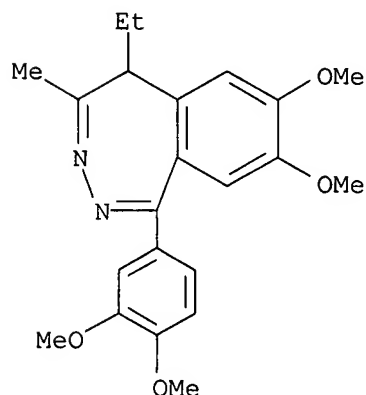
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 10 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 867020-89-1 REGISTRY

ED Entered STN: 09 Nov 2005
 CN Carbonic acid, dilithium salt, mixt. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI) (CA INDEX NAME)
 MF C22 H26 N2 O4 . C H2 O3 . 2 Li
 CI MXS
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

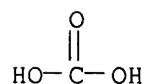
CM 1

CRN 22345-47-7
 CMF C22 H26 N2 O4



CM 2

CRN 554-13-2 (463-79-6)
 CMF C H2 O3 . 2 Li

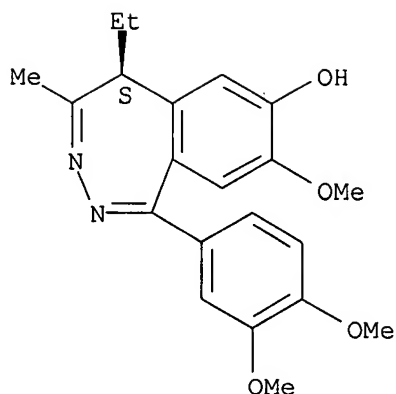


● 2 Li

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 11 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
 RN 792950-07-3 REGISTRY
 ED Entered STN: 06 Dec 2004
 CN 5H-2,3-Benzodiazepin-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-, (5S)- (CA INDEX NAME)
 OTHER NAMES:
 CN (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
 FS STEREOSEARCH
 MF C21 H24 N2 O4
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

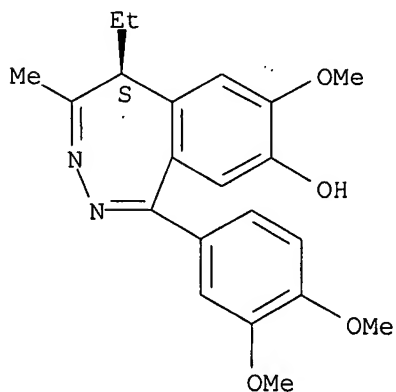


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 12 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 702693-86-5 REGISTRY
ED Entered STN: 02 Jul 2004
CN **5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)-** (CA INDEX NAME)
OTHER NAMES:
CN **(S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine**
FS STEREOSEARCH
MF C21 H24 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 13 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 697754-53-3 REGISTRY
ED Entered STN: 23 Jun 2004
CN **5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-**

4-methyl-, (5R)- (CA INDEX NAME)

OTHER NAMES:

CN (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine

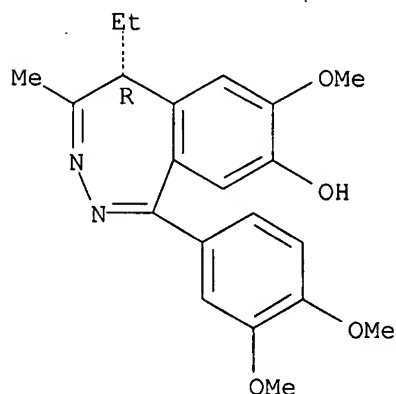
FS STEREOSEARCH

MF C21 H24 N2 O4

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1907 TO DATE)

9 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 14 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 697754-50-0 REGISTRY

ED Entered STN: 23 Jun 2004

CN 5H-2,3-Benzodiazepin-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-, (5R)- (CA INDEX NAME)

OTHER NAMES:

CN (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine

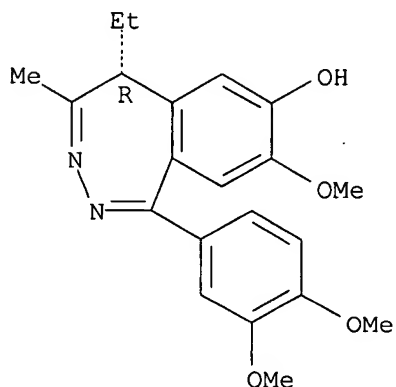
FS STEREOSEARCH

MF C21 H24 N2 O4

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)

8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

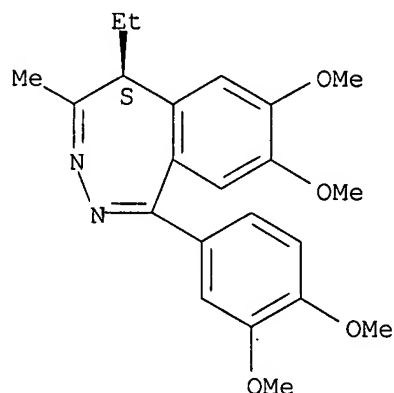
L3 ANSWER 15 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 476625-22-6 REGISTRY
ED Entered STN: 18 Dec 2002
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, (2S,3S)-, compd. with
(5S)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-
benzodiazepine (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . x C18 H14 O8
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

CM 1

CRN 82059-51-6

CMF C22 H26 N2 O4

Absolute stereochemistry.

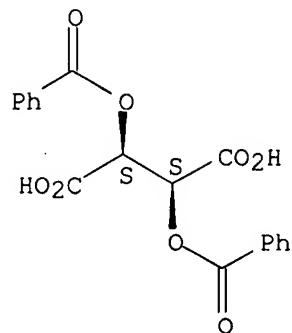


CM 2

CRN 17026-42-5

CMF C18 H14 O8

Absolute stereochemistry. Rotation (+).



1 REFERENCES IN FILE CA (1907 TO DATE)

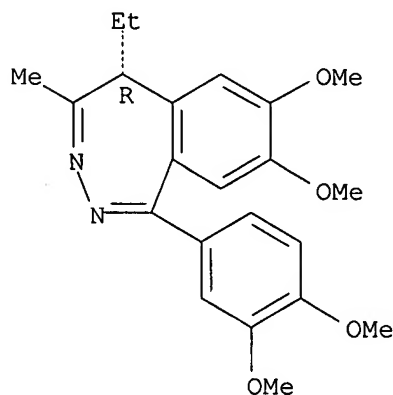
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 16 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
 RN 476625-20-4 REGISTRY
 ED Entered STN: 18 Dec 2002
 CN Butanedioic acid, 2,3-bis(benzoyloxy)-, (2R,3R)-, compd. with
 (5R)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-
 benzodiazepine (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C22 H26 N2 O4 . x C18 H14 O8
 SR CA
 LC STN Files: CA, CAPLUS, IMSRESEARCH, USPAT2, USPATFULL

CM 1

CRN 82059-50-5
 CMF C22 H26 N2 O4

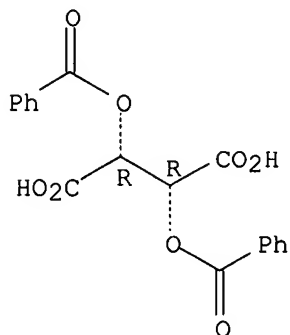
Absolute stereochemistry.



CM 2

CRN 2743-38-6
 CMF C18 H14 O8

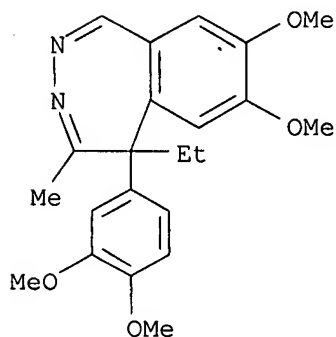
Absolute stereochemistry. Rotation (-).



1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

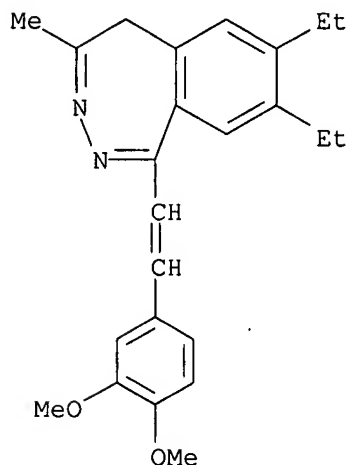
L3 ANSWER 17 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
 RN 344259-20-7 REGISTRY
 ED Entered STN: 01 Jul 2001
 CN 5H-2,3-Benzodiazepine, 5-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-

4-methyl- (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4
SR Reaction Database



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 ANSWER 18 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 181515-97-9 REGISTRY
ED Entered STN: 03 Oct 1996
CN 5H-2,3-Benzodiazepine, 1-[2-(3,4-dimethoxyphenyl)ethenyl]-7,8-diethyl-4-methyl- (9CI) (CA INDEX NAME)
MF C24 H28 N2 O2
SR CA
LC STN Files: CA, CAPLUS

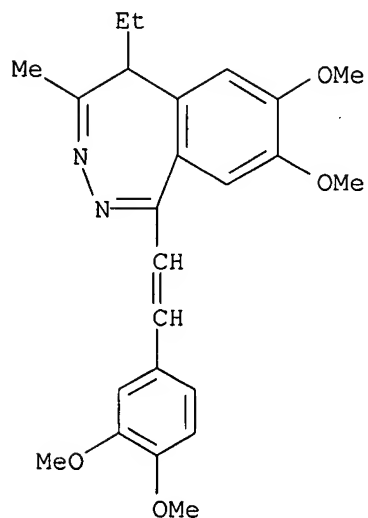


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 19 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 181120-58-1 REGISTRY
ED Entered STN: 24 Sep 1996
CN 5H-2,3-Benzodiazepine, 1-[2-(3,4-dimethoxyphenyl)ethenyl]-5-ethyl-7,8-dimethoxy-4-methyl- (9CI) (CA INDEX NAME)
MF C24 H28 N2 O4

SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

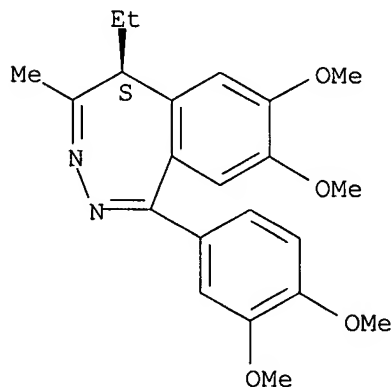
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 20 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 109575-89-5 REGISTRY
ED Entered STN: 01 Aug 1987
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-, monomethanesulfonate (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS

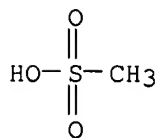
CM 1

CRN 82059-51-6
CMF C22 H26 N2 O4

Absolute stereochemistry.



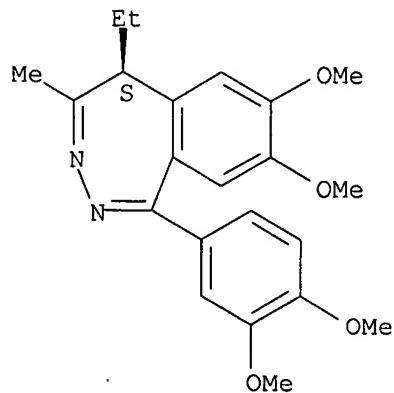
CM 2
CRN 75-75-2
CMF C H4 O3 S



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 21 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 109575-88-4 REGISTRY
ED Entered STN: 01 Aug 1987
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrochloride, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . Cl H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)
CRN (82059-51-6)

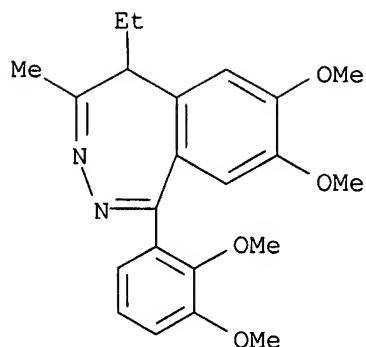
Absolute stereochemistry.



● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 22 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 104346-54-5 REGISTRY
ED Entered STN: 21 Sep 1986
CN 5H-2,3-Benzodiazepine, 1-(2,3-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 23 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 100346-56-3 REGISTRY

ED Entered STN: 22 Feb 1986

CN Methanol, compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, compd. with methanol (9CI)

MF C22 H26 N2 O4 . x C H4 O

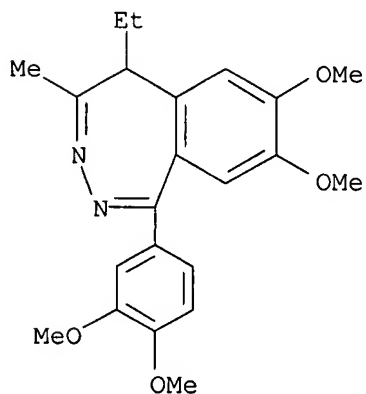
SR CA

LC STN Files: CA, CAPLUS, IMSRESEARCH

CM 1

CRN 22345-47-7

CMF C22 H26 N2 O4



CM 2

CRN 67-56-1

CMF C H4 O

H₃C-OH

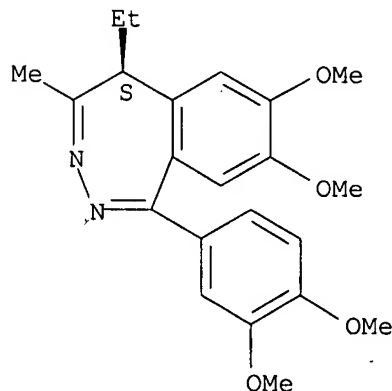
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 24 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 98168-49-1 REGISTRY
ED Entered STN: 22 Sep 1985
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrobromide, (S)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN (-)-Tofizopam bromide
FS STEREOSEARCH
MF C22 H26 N2 O4 . Br H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)
CRN (82059-51-6)

Absolute stereochemistry.



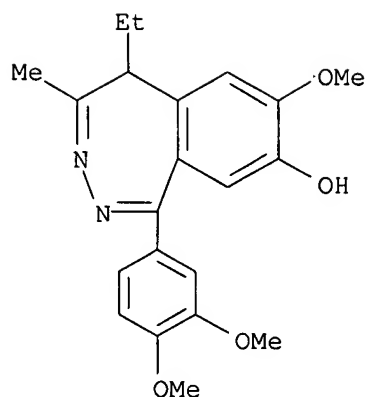
● HBr

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 25 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 95500-09-7 REGISTRY
ED Entered STN: 23 Mar 1985
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (CA INDEX NAME)

OTHER NAMES:

CN 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
MF C21 H24 N2 O4
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10 REFERENCES IN FILE CA (1907 TO DATE)

10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 26 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

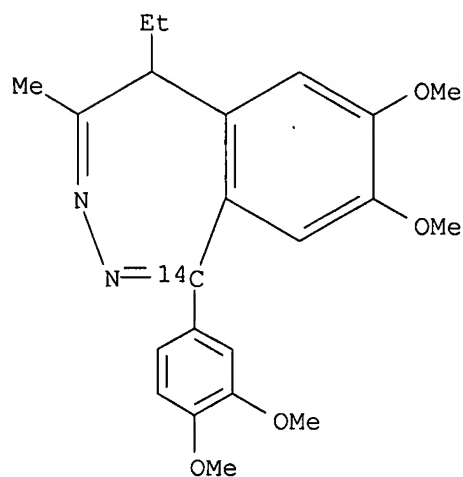
RN 93635-47-3 REGISTRY

ED Entered STN: 18 Dec 1984

CN **5H-2,3-Benzodiazepine-1-14C, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)

MF C22 H26 N2 O4

LC STN Files: CA, CAPLUS, CASREACT



1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 27 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 90140-61-7 REGISTRY

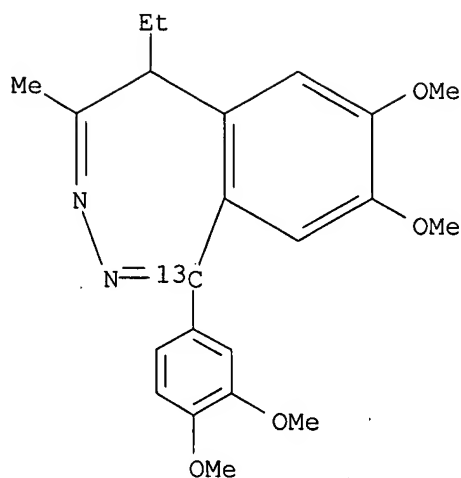
ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine-1-13C, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)

MF C22 H26 N2 O4

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT

(*File contains numerically searchable property data)



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 28 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 89664-97-1 REGISTRY

ED Entered STN: 16 Nov 1984

CN Thiocyanic acid, compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (1:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monothiocyanate (9CI)

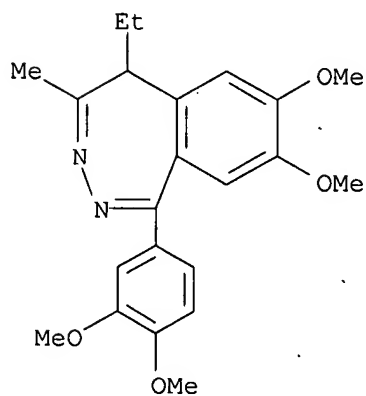
MF C22 H26 N2 O4 . C H N S

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH
(*File contains numerically searchable property data)

CM 1

CRN 22345-47-7

CMF C22 H26 N2 O4



CM 2

CRN 463-56-9

CMF C H N S

HS-C≡N

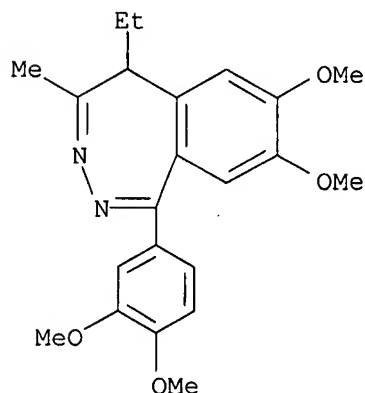
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 29 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 89664-96-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, sulfate (1:1) (9CI) (CA INDEX NAME)**
MF C22 H26 N2 O4 . H2 O4 S
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH
(*File contains numerically searchable property data)

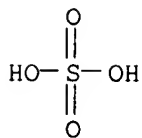
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 7664-93-9
CMF H2 O4 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

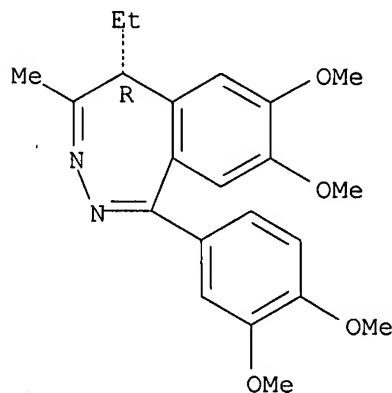
L3 ANSWER 30 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 87584-92-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)**
OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)
FS STEREOSEARCH
MF C22 H26 N2 O4 . C4 H6 O6
LC STN Files: CA, CAPLUS, IMSRESEARCH

CM 1

CRN 82059-50-5
CMF C22 H26 N2 O4

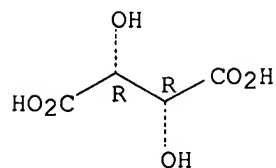
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 31 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82339-97-7 REGISTRY
ED Entered STN: 16 Nov 1984

CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with
(S)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-
benzodiazepine (1:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-, [R-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1) (9CI)

FS STEREOSEARCH

MF C22 H26 N2 O4 . C18 H14 O8

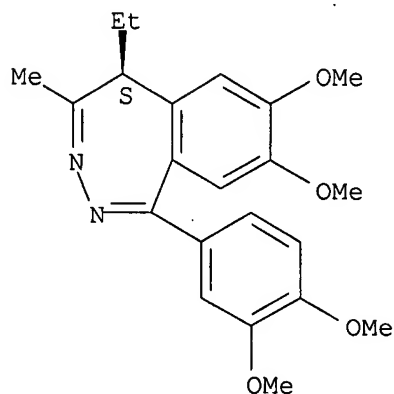
LC STN Files: BEILSTEIN*, CA, CAPLUS

(*File contains numerically searchable property data)

CM 1

CRN 82059-51-6
CMF C22 H26 N2 O4

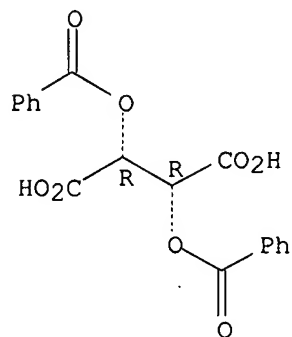
Absolute stereochemistry.



CM 2

CRN 2743-38-6
CMF C18 H14 O8

Absolute stereochemistry. Rotation (-).



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 32 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 82339-96-6 REGISTRY

ED Entered STN: 16 Nov 1984

CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with
(R)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-
benzodiazepine (1:1) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
4-methyl-, (R)-, [R-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1)
(9CI)

FS STEREOSEARCH

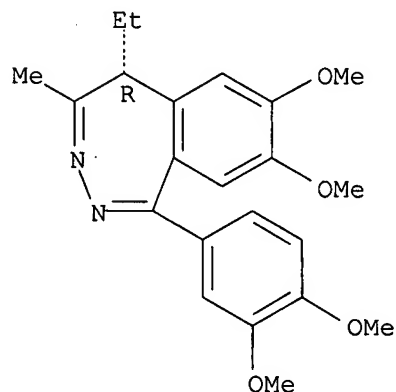
MF C22 H26 N2 O4 . C18 H14 O8

LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH
(*File contains numerically searchable property data)

CM 1

CRN 82059-50-5
CMF C22 H26 N2 O4

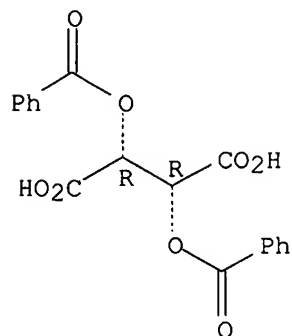
Absolute stereochemistry.



CM 2

CRN 2743-38-6
CMF C18 H14 O8

Absolute stereochemistry. Rotation (-).

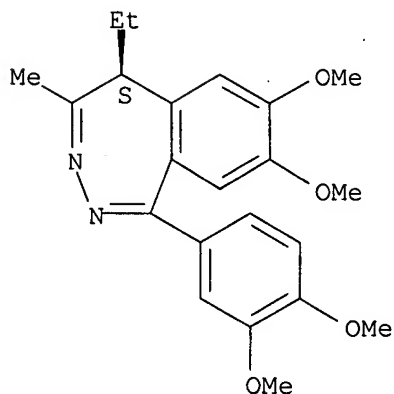


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 33 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82059-51-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5S)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-
OTHER NAMES:
CN (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
CN (S)-Tofisopam
CN Levotofisopam
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

31 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

31 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 34 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 82059-50-5 REGISTRY

ED Entered STN: 16 Nov 1984

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5R)- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-

OTHER NAMES:

CN (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine

CN (R)-Tofisopam

CN Dextofisopam

FS STEREOSEARCH

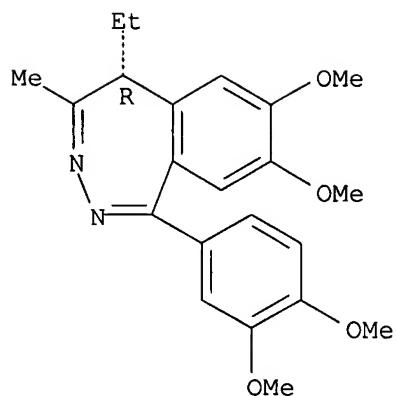
MF C22 H26 N2 O4

CI COM

LC STN Files: ADISINSIGHT, BEILSTEIN*, CA, CAPLUS, CBNB, IMSDRUGNEWS, IMSRESEARCH, PHAR, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

34 REFERENCES IN FILE CA (1907 TO DATE)

34 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 35 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 82005-40-1 REGISTRY

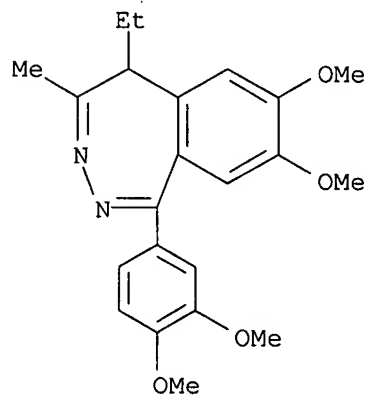
ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, labeled with deuterium (9CI) (CA INDEX NAME)**

MF C22 H26 N2 O4

LC STN Files: CA, CAPLUS

IL XH-2



1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 36 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

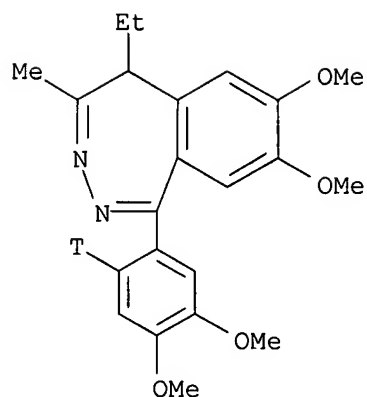
RN 82005-36-5 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(4,5-dimethoxyphenyl)-2-t)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI) (CA INDEX NAME)**

MF C22 H25 N2 O4 T

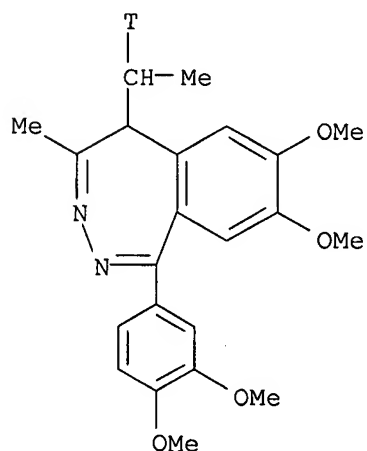
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

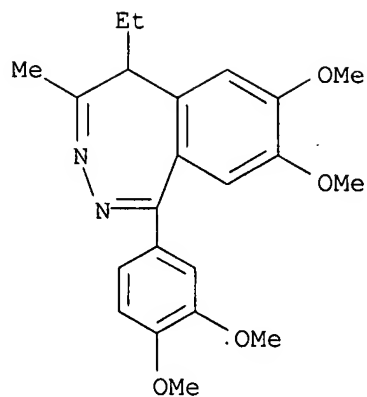
L3 ANSWER 37 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82005-31-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-(ethyl-1-t)-7,8-dimethoxy-4-methyl-, (9CI)** (CA INDEX NAME)
MF C22 H25 N2 O4 T
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

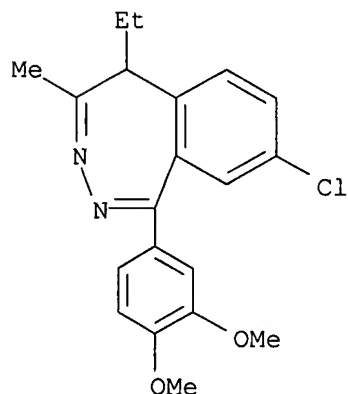
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 38 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 79137-03-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, labeled with carbon-14 (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
LC STN Files: CA, CAPLUS
IL XC-14



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

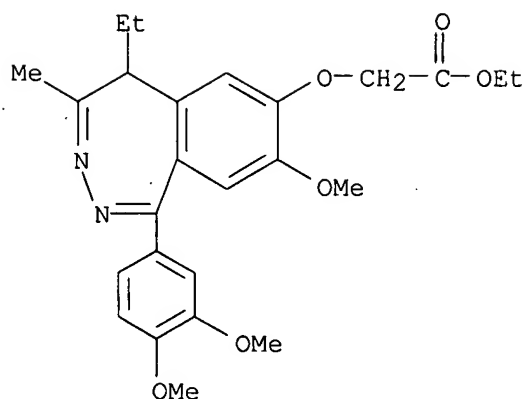
L3 ANSWER 39 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 75113-95-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 8-chloro-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl- (9CI)** (CA INDEX NAME)
MF C20 H21 Cl N2 O2
LC STN Files: CA, CAPLUS, USPATFULL



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 40 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-46-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Acetic acid, [[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-, ethyl ester (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, acetic acid deriv.**
MF C25 H30 N2 O6
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)

4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 41 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

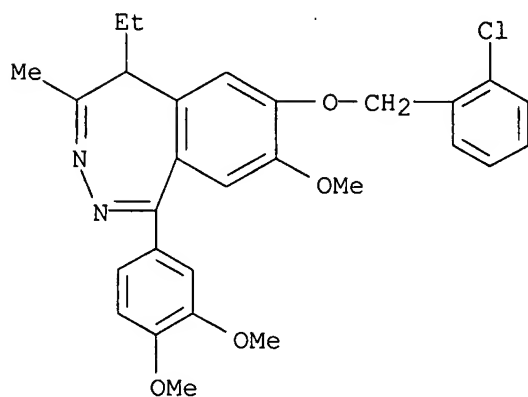
RN 74950-45-1 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 7-[(2-chlorophenyl)methoxy]-1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl- (9CI)** (CA INDEX NAME)

MF C28 H29 Cl N2 O4

LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)

4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 42 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 74950-44-0 REGISTRY

ED Entered STN: 16 Nov 1984

CN **Ethanamine, 2-[[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-N,N-diethyl-, dihydrochloride (9CI)** (CA INDEX NAME)

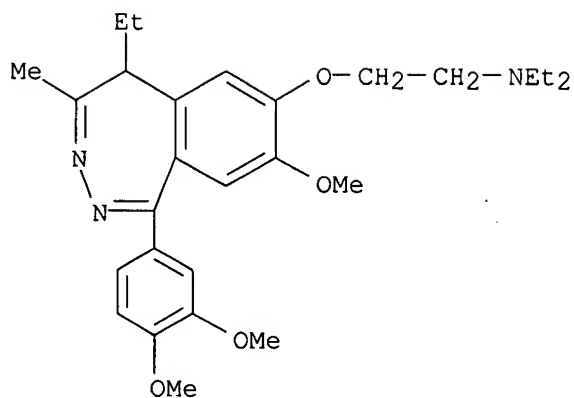
OTHER CA INDEX NAMES:

CN **5H-2,3-Benzodiazepine, ethanamine deriv.**

MF C27 H37 N3 O4 . 2 Cl H

LC STN Files: CA, CAPLUS, USPATFULL

CRN (767237-74-1)



● 2 HCl

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 43 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

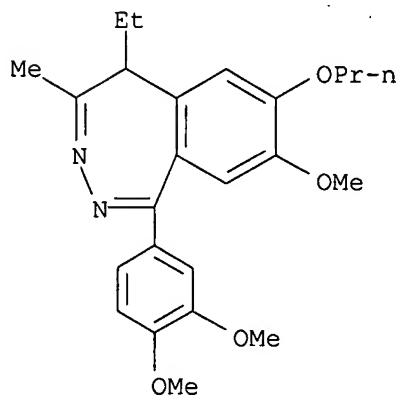
RN 74950-43-9 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-propoxy- (9CI)** (CA INDEX NAME)

MF C24 H30 N2 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 44 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

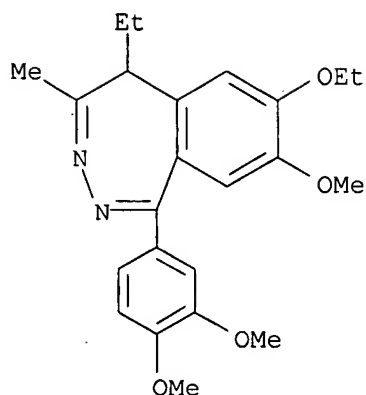
RN 74950-42-8 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7-ethoxy-5-ethyl-8-methoxy-4-methyl- (9CI)** (CA INDEX NAME)

MF C23 H28 N2 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 45 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

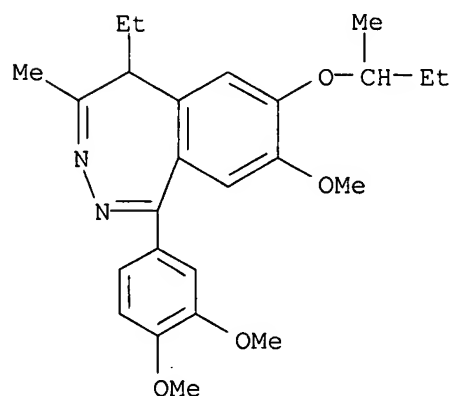
RN 74950-41-7 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-(1-methylpropoxy)- (9CI)** (CA INDEX NAME)

MF C25 H32 N2 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 46 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 74950-40-6 REGISTRY

ED Entered STN: 16 Nov 1984

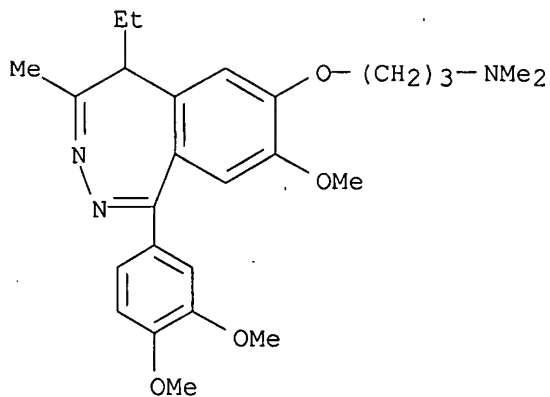
CN **1-Propanamine, 3-[[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-N,N-dimethyl- (9CI)** (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN **5H-2,3-Benzodiazepine, 1-propanamine deriv.**

MF C26 H35 N3 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 47 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

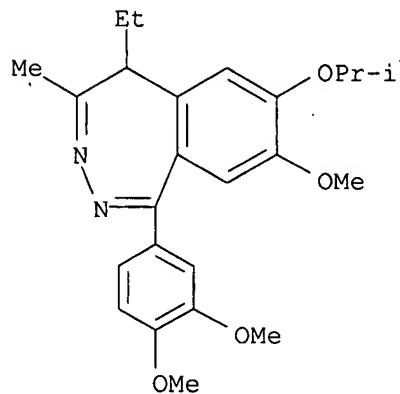
RN 74950-39-3 REGISTRY

ED Entered STN: 16 Nov 1984

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-(1-methylethoxy)- (9CI) (CA INDEX NAME)

MF C24 H30 N2 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 48 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

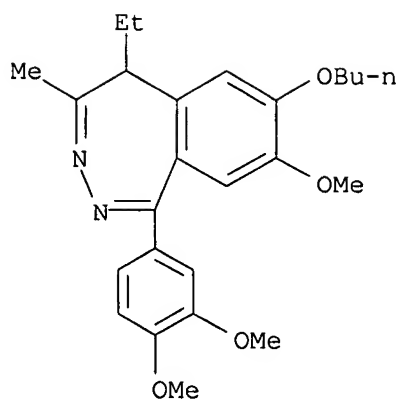
RN 74950-38-2 REGISTRY

ED Entered STN: 16 Nov 1984

CN 5H-2,3-Benzodiazepine, 7-butoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl- (9CI) (CA INDEX NAME)

MF C25 H32 N2 O4

LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 49 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

RN 74950-18-8 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-** (CA INDEX NAME)

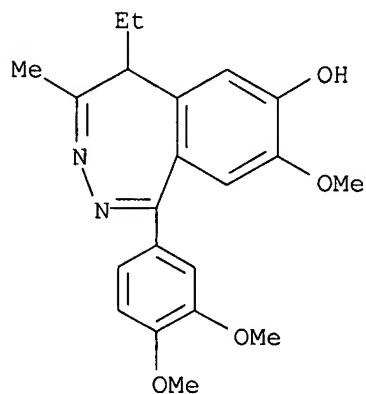
OTHER NAMES:

CN **1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine**

MF C21 H24 N2 O4

CI COM

LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)

15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 50 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN

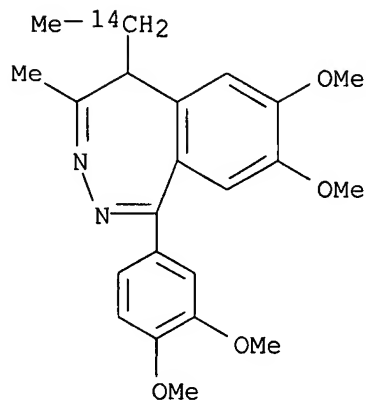
RN 55293-93-1 REGISTRY

ED Entered STN: 16 Nov 1984

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-(ethyl-1-14C)-7,8-dimethoxy-4-methyl-** (9CI) (CA INDEX NAME)

MF C22 H26 N2 O4

LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

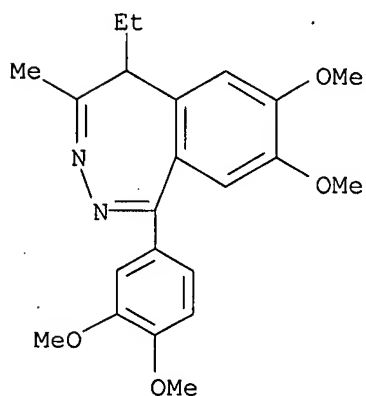


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 51 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-10-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2-Naphthalenol, 4-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-,
compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-
benzodiazepine (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
4-methyl-, compd. with 4-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-2-
naphthalenol (1:1) (9CI)
MF C22 H26 N2 O4 . C22 H24 O5
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)

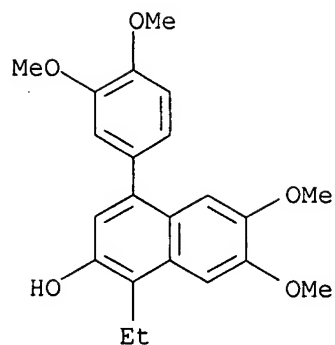
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CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 15462-94-9
CMF C22 H24 O5

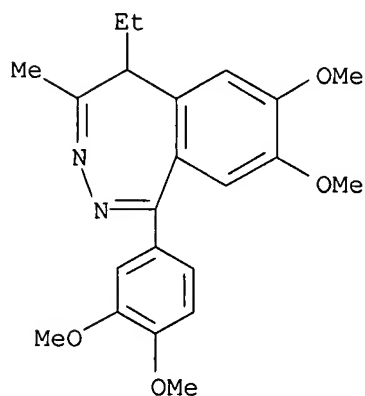


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 52 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-08-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, compd. with 2,4,6-trinitrophenol (1:1) (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4 . C6 H3 N3 O7
LC STN Files: CA, CAPLUS, IMSRESEARCH, USPATFULL

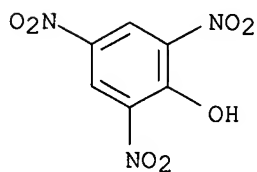
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 88-89-1
CMF C6 H3 N3 O7

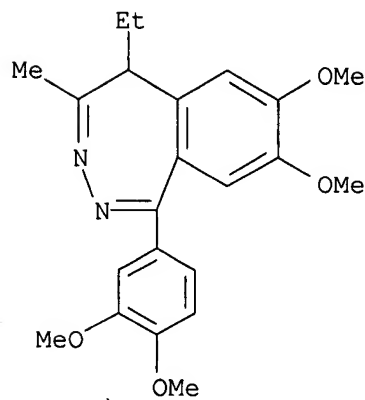


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 53 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-07-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monoperchlorate (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Cl H O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)

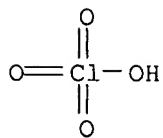
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CRN 22345-47-7
CMF C22 H26 N2 O4 .



CM 2

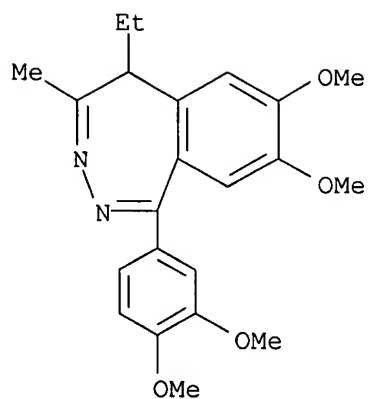
CRN 7601-90-3
CMF Cl H O4



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 54 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-06-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrobromide (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Br H
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)
CRN (22345-47-7)

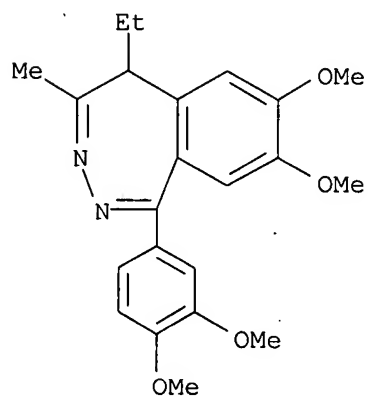


● HBr

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 55 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-05-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrochloride (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)
CRN (22345-47-7)



● HCl

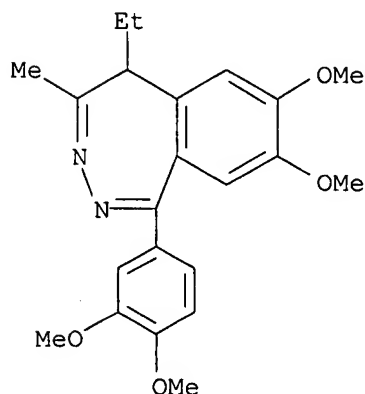
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4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 56 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
 RN 28710-23-8 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, picrate (8CI) (CA INDEX NAME)
 MF C22 H26 N2 O4 . x C6 H3 N3 O7
 LC STN Files: CA, CAPLUS, IFICDB, IFIPAT, IFIUDB, IMSRESEARCH, USPATOLD

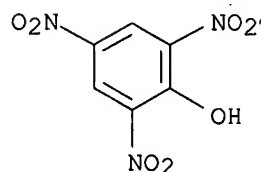
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CRN 22345-47-7
 CMF C22 H26 N2 O4



CM 2

CRN 88-89-1
 CMF C6 H3 N3 O7



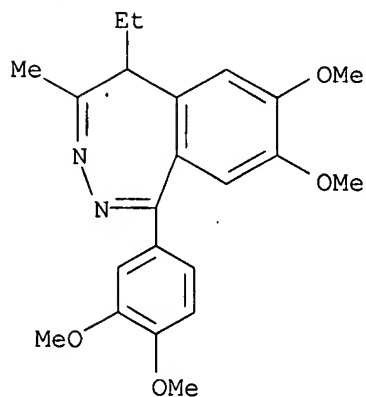
1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 57 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
 RN 22345-47-7 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

OTHER NAMES:

CN 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
 CN 7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5H-2,3-benzodiazepine
 CN EGYT 341
 CN Grandaxin
 CN Seriel
 CN Tofisopam
 DR 87555-18-8
 MF C22 H26 N2 O4

CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
 BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM,
 DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS,
 IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SPECINFO,
 TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

211 REFERENCES IN FILE CA (1907 TO DATE)
 5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 211 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus
 COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
162.90	163.11

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 22:35:22 ON 27 SEP 2007
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 FILE LAST UPDATED: 26 Sep 2007 (20070926/ED)

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<http://www.cas.org/infopolicy.html>

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      5 22345-47-7D
    209 22345-47-7/RN
        (22345-47-7 (NOTL) 22345-47-7D )
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L7      ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:      2004:681397  CAPLUS
DOCUMENT NUMBER:       141:167829
TITLE:                 Method of lowering body temperature
                        with (S)-tofisopam
INVENTOR(S):           Harris, Herbert W.; Kucharik, Robert F.
PATENT ASSIGNEE(S):    USA
SOURCE:                U.S. Pat. Appl. Publ., 14 pp.
                        CODEN: USXXCO
DOCUMENT TYPE:         Patent
LANGUAGE:              English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004162284	A1	20040819	US 2003-369823	20030219
WO 2004073638	A2	20040902	WO 2004-US4726	20040217
WO 2004073638	A3	20050113		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004224943	A1	20041111	US 2004-827839	20040419

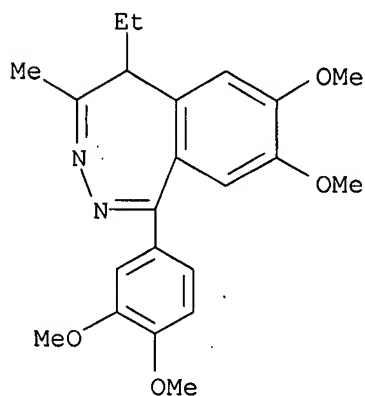
PRIORITY APPLN. INFO.: US 2003-369823 A 20030219
US 2004-781422 A2 20040217

AB (S)-**Tofisopam**, substantially isolated from the corresponding (R)-enantiomer of **tofisopam**, is administered to lower the **body temp.** of an individual.

IT **22345-47-7, Tofisopam**
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(resolution of; (S)-**tofisopam** for lowering **body temp.**)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:964818 CAPLUS

DOCUMENT NUMBER: 141:410972

TITLE: Preparation of (R)-2,3-benzodiazepine derivatives and method of lowering **body temperature** with them

INVENTOR(S): Leventer, Steven M.; Kucharik, Robert F.

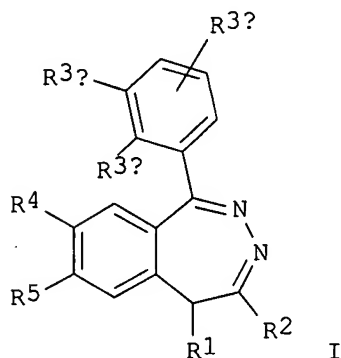
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 781,422.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224943	A1	20041111	US 2004-827839	20040419
US 2004162284	A1	20040819	US 2003-369823	20030219
US 20042229866	A1	20041118	US 2004-781422	20040217
PRIORITY APPLN. INFO.:			US 2003-369823	A2 20030219
			US 2004-781422	A2 20040217
OTHER SOURCE(S):	MARPAT 141:410972			
GI				



AB An (R)-2,3-benzodiazepine of formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3a, R3b, R3c = H, -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halogen; provided at least one of R3a, R3b and R3c is other than H; R4, R5 = -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halo; or R4 and R5 may combine to form a 5-, 6- or 7-membered heterocyclic ring], substantially free from the corresponding (S)-enantiomer thereof with respect to the absolute conformation at the 5-position of the benzodiazepine ring, is administered to lower the **body temp.** of an individual. More specifically, the administered compound is (R)-**tofisopam**, or a pharmaceutically-acceptable salt thereof and said individual is afflicted with a disorder associated with an elevated **body temp.** such as fever, malignant hyperthermia, serotonin syndrome, or hot flashes during menopause or perimenopause or occurred as side effects of drug therapy or subsequent to the removal of estrogen-producing tissue. Furthermore said individual is afflicted with a disorder such as cerebral ischemia or stroke wherein therapeutic benefit is achieved by lowering of the **body temp.** to a level below the normal **body temp.** Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride was dissolved in methanol (35 mL) at 40°, cooled to 20-25°, treated with a solution of hydrazine hydrate (0.75 g, 15 mmol) in 5 mL methanol, and allowed to reaction. The reaction was monitored by HPLC and when complete, was evaporated to dryness. The residue is triturated with cold water (3 mL), filtered, and dried to yield crude (RS)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**). Racemic **tofisopam** was resolved by chiral chromatog. using a semipreparative Chirobiotic V column (ASTEC, Whippany, New Jersey) and Me tert-Bu ether/MeCN as the eluent to give (R)-**tofisopam** and (S)-

tofisopam. In a stress induced hyperthermia assay using mice, racemic **tofisopam** demonstrated activity in lowering the core **body temp**. (S)-**tofisopam** was more active than either the racemate or the (R)-enantiomer. However, the (R)-enantiomer showed greater tolerability compared with either the racemate or the (S)-enantiomer. For example, the mice treated with the (R)-enantiomer showed less sedation, abnormal gait, or ptosis, decreased muscle tone, decreased lacrimation, or decreased reactivity to touch compared with either (S)-enantiomer or the racemate.

L7 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:577894 CAPLUS
DOCUMENT NUMBER: 145:62931
TITLE: Method of isolating (R)-**tofisopam**
INVENTOR(S): Perrin, Scott R.; Ye, Naidong; Galbraith, Kimm B.; Hauck, Wilhelm
PATENT ASSIGNEE(S): Vela Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Ser. No. 841,075.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

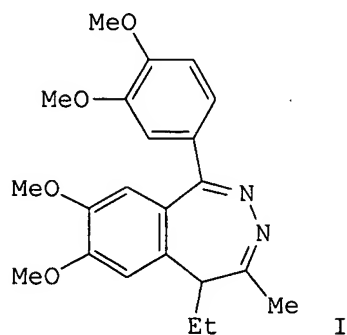
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006128955	A1	20060615	US 2005-305490	20051215
US 2004254174	A1	20041216	US 2004-841075	20040507
US 7265106	B2	20070904		
WO 2007078808	A2	20070712	WO 2006-US47656	20061213
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			

PRIORITY APPLN. INFO.:
US 2003-469456P P 20030509
US 2004-841075 A2 20040507
US 2005-305490 A 20051215

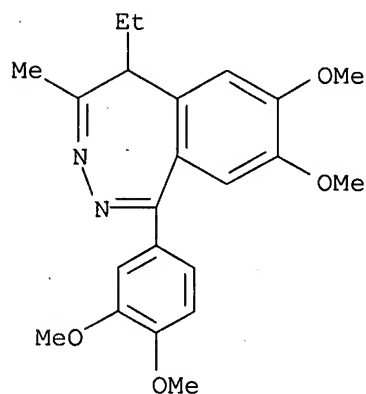
AB The present invention is directed to a process for the isolation of (R)-**tofisopam** with high enantiomeric purity and high overall yields from a mixture of **tofisopam** enantiomers by means of a non-steady state continuous chromatog. process. Isolation of (R)-**tofisopam** from a mixture of **tofisopam** enantiomers, i.e. (R)-(-), R(+)-, (S)-(-)-, and (S)-(+)-**tofisopam**, was carried out in a nonsteady state continuous separation process (VariCol process) using 5 2.5 cm (i.d.)+10.6 cm chromatog. columns packed with CHIRALPAK 61161, a chiral separation medium comprising amylose tris(3-chloro-4-methylbenzoate) coated on silica, which were connected in series in a loop. Multiple inlets and outlets were placed in the loop between the columns. After the system was stabilized by passing MeCN through the columns, a solution of **tofisopam** enantiomers in MeCN (concentration 48-50 g/L) was continuously injected into the system. The separation was performed using the various temps., feed concns. and flow rates to give 78.3% (highest yield) (R)-**tofisopam** (highest purity 99.5%).

L7 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1979:34556 CAPLUS
 DOCUMENT NUMBER: 90:34556
 TITLE: Analytical investigation of **tofisopam**
 AUTHOR(S): Benko, Andras
 CORPORATE SOURCE: Orsz. Igazságügyi Vegyeszeti Intéz., Budapest, Hung.
 SOURCE: Acta Pharmaceutica Hungarica (1978), 48(6), 241-5
 CODEN: APHGAO; ISSN: 0001-6659
 DOCUMENT TYPE: Journal
 LANGUAGE: Hungarian
 GI



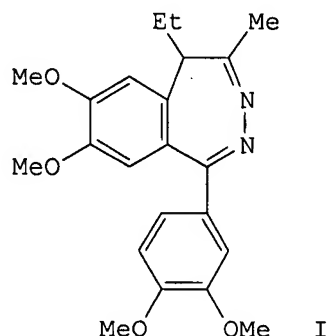
AB Methods are given for the detection and determination of **Grandaxin** (**tofisopam**) (I) [22345-47-7] in forensic medicine. Seven solvents, described in the literature, were compared for the thin-layer chromatog. separation of I from diazepam and nitrazepam. Gas chromatog. was carried out on OV-101 on Gaschrom Q, using a flame-ionization detector and N carrier gas. The column temp. was 310°. The determination threshold was 1 µg. For UV spectrophotometry, the anal. line was 311 nm.
 IT 22345-47-7
 RL: ANT (Analyte); ANST (Analytical study)
 (determination of, in legal chemical)
 RN 22345-47-7 CAPLUS
 CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
 ACCESSION NUMBER: 1983:499217 CAPLUS
 DOCUMENT NUMBER: 99:99217
 TITLE: **Tofisopam**, a new 2,3-benzodiazepine.

Inhibition of changes induced by stress loading and hypothalamic stimulation

AUTHOR(S): Yamaguchi, K.; Suzuki, K.; Niho, T.; Shimora, M.; Ito, C.; Ohnishi, H.
CORPORATE SOURCE: Fuji Cent. Res. Lab., Mochida Pharm. Co., Ltd., Gotemba, 412, Japan
SOURCE: Canadian Journal of Physiology and Pharmacology (1983), 61(6), 619-25
CODEN: CJPPA3; ISSN: 0008-4212
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Effects of **tofisopam** (I) [22345-47-7] on gastric ulceration induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats were investigated along with propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to elec. stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and γ -oryzanol. **Tofisopam** (30 and 100 mg/kg, orally) inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced an increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam**. **Tofisopam** (1.0 mg/kg, i.v., or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe temp., and mydriasis induced by elec. stimulation of the medial hypothalamic area in rabbits. However, diazepam and γ -oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. Thus, **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

IT 22345-47-7

RL: BIOL (Biological study)

(hypothalamus stimulation- and stress-induced changes response to)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

Use of health services by the climacteric women in primary health care: The need for an integral approach

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Pedro Arango Fernández³ & Juan Martín Tello³

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(Cádiz), Spain

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Abstract. During the climacteric, women experience multiple health problems. As their needs are not catered for in an integral fashion due to the lack of any specific programme or mechanism to provide for this, they show an increased use of the health services, and an increased rate of referrals to different specialists. This study, carried out in a Basic Health Zone in San Fernando (Cádiz, Andalucía, Spain) on a sample of climacteric women who attended the Health Centre during 1995, examines these points and shows a significantly higher use of the health services in relation to the rest of the female population (those who are not in the climacteric age group) as well as a high percentage of referrals (74.6%) to specialists. It was found that both the level of knowledge about the

climacteric and the use of the health services influenced by the educational level ($p < 0.001$ age ($p < 0.05$). Women who felt that their families provided an understanding and supportive atmosphere were found to have less psychological problems consequently, less consultations and referrals for any reason ($p < 0.00001$). The authors hope that findings will provide a basis for the setting up of a programme of integral health care for climacteric women at the level of primary health care. Careful planning and the drawing up of a strategic plan, it would be possible to provide for the needs of this population group in a more satisfactory way. It would also permit a rationalization of the resources available.

Key words: Climacteric, Health promotion, Level of knowledge, Use of health services

Introduction

Both the directives issued by the Spanish Ministry of Health and Consumption and the Health Plan for Andalucía contemplate the possibility of providing integral and protocolised care for climacteric women at the level of primary health care (Health Plan for Andalucía, 1993).

In reality, however, each symptom is dealt with separately under different subprograms. It is only at the tertiary level in the Spanish Health Services that we find specific menopause units and, due to the high level of specialisation and the difficulty of access, these usually have a low level of catchment (1.5% in Cádiz, Andalucía, Spain in 1995).

worthy of attention given that more than a third of the total female population will belong to this group and that it constitutes a considerable period of a woman's life during which she is suffering from corresponding symptoms and health problems.

During this time women usually experience a number of symptoms and disorders attributable to the decline in the endocrine function of the ovaries. Authors such as Bedoya, Fritz, Jones, and Noller [4–7] speak of 'short term' symptoms (hot flashes, menstrual irregularities, insomnia, anxiety, depression), 'medium term' symptoms, especially gynaecological (sexual decline of libido, painful sexual intercourse) and urinary tract problems (urinary incontinence, urinary infection among others) and 'long term' symptoms, particularly osteoporosis and cardio-

at the level of Primary Health Care, to provide them with easier access to solutions for their health problems.

The study, which is descriptive, was based on a small area, the Basic Health Zone (BHZ) Rodríguez Arias in San Fernando (Cádiz, Andalucía, Spain) which is fully identifiable from a geographic, demographic and epidemiological point of view, covering a population of 25,000 inhabitants (32% of the population of San Fernando). The demographic characteristics of this Basic Health Zone are representative of other Basic Health Zones, not only in the province of Cádiz, but also Andalucía.

The Health Centre is staffed by general practitioners, pediatricians, nurses, one social worker, one veterinary surgeon and auxiliary staff. The specialist consultants, including gynaecologists are in the main public hospital 'Puerta del Mar', which is 10 km away from the Health Centre, and has a Menopause Unit.

The aims of the study were:

1. To ascertain the average age of the climacteric women in the BHZ studied.
2. To ascertain the degree of use of health services by the women in the BHZ, aged from 40–57 years (climacteric), and the non-climacteric female population (12–39 years and 58 years plus) during 1995.
3. To consider some of the variables which may lead to a greater or lesser use of the health services, such as age and educational level.
4. To determine the principal motives which lead these women to consult their doctor.
5. To determine the degree of referrals of the climacteric women studied to other levels of the health service.
6. To determine the level of knowledge about the climacteric of the climacteric women in the BHZ and the possible relation with their use of the health services, their educational level and their age.
7. To determine how much family support these women receive and to evaluate what influence this factor may have on the appearance of psychological disorders and related medical consultations.

Materials and methods

A descriptive, correlational study was carried out for

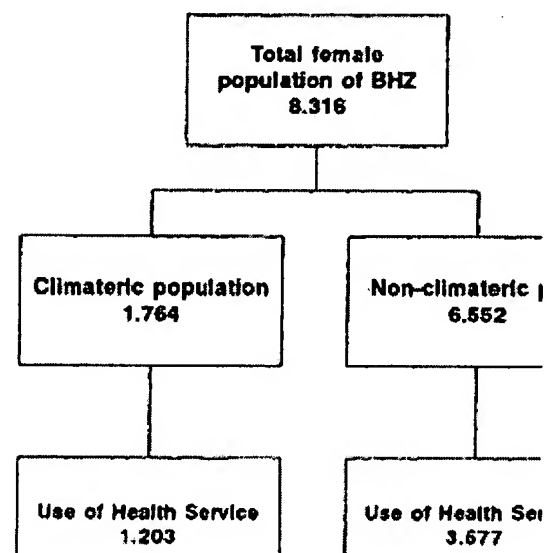
1.764% climacteric women and 6.552% non climacteric women (12–39 years or 58 years plus) though the group of non-climacteric women covers a wide age range, adolescents and women over 58 years represent a low percentage of the population corresponding to the Rodríguez Arias Health Centre and their consultations were minimal (the latter because of their generally good state of health and the former because they have a higher percentage of home visits). For this reason possible distortion of the results due to the wide age range is minimal. The vast majority of the women who consulted their doctor at the Health Centre were between 30 and 50 years of age.

From the appointment records of the Rodríguez Arias Health Centre for 1995, information was obtained corresponding to the women in each group who had used the health services, that is, the women who consulted their family doctor in the Health Centre. This was the reference population for the study from which the sample was taken.

The calculation of the size of the sample was done with a computer aided (Epi-Info 5.0) using this group of women for an expected frequency of 50% and a confidence interval of 95%. There were found 291 climacteric women and 347 non-climacteric women.

Subsequently, sample women were selected randomly from the appointment records for each group to be studied (Figure 1).

A form was drawn up to include: personal information (age and educational level, among



ers), reasons for consultation, referrals and reasons for the same, excluding the usual screening for the age group. This data was obtained from the monitoring sheets in the clinical histories of the women to be studied.

The information referring to the non-climacteric sample of the population, which was taken from the appointment records of the Health Centre for 1995, was limited by the number of consultations made for that year.

A questionnaire was also drawn up comprising a series of questions to ascertain the level of knowledge of the women in the sample about the climacteric, including: the age at which the climacteric usually begins, accompanying symptoms and their identification, the existence of treatment and if they had requested it.

In anticipation of the possible answers to these questions, three levels were established to reflect the level of knowledge:

- low: 0-3 correct answers.
- medium: 4-7 correct answers.
- high: 8-11 correct answers.

The questionnaire also covered information about the climacteric that the women had received from their doctors, and if they felt that their family were supportive and understanding.

Once the questionnaire had been drawn up it was validated and no corrections were found to be necessary. The questionnaire was applied to the 291 selected climacteric women during home visits by 4 doctors and one nurse, having previously agreed on the criteria and procedure to be followed.

The information obtained was processed with the aid of a computer (Epi-Info 5.0).

For the comparison of the proportions, the χ^2 test with the correction of Yates was used to obtain a confidence interval of 99%. Anova and Bartlett's test of homogeneity and variance were also applied for the comparison of averages when they were considered necessary.

Results

The total population of climacteric women belonging to the Health Centre who consulted their doctor in 1995 on at least one occasion was 1203 (68%), generating 13,582 visits, whereas the number of women of the non-climacteric population over 12

The average age of the climacteric women was 47 years with a standard deviation of 1.5 years.

Regarding the educational level of the women, 27.9% (79 women) had no schooling, 40.7% (119 women) had primary education, 21.9% (62 women) had secondary education and 9.6% (27 women) received further and/or university education.

An Anova test, to compare the average use of health services with the educational level of the women showed that those with a higher educational level used the health services less versus no-schooling, primary-education and secondary-education ($p < 0.01$).

Bartlett's homogeneity of the variance showed that the average use of the health services varied significantly according to the age of the woman, and younger women used the health services ($p < 0.01$).

The principal motives for consultation with a family doctor are shown in Table 1, where we can see that rheumatic symptoms (pains in the joints) were the prime reason for 591 visits (18.5%), followed by cardiovascular pathology (principally high blood pressure and alterations in the heart beat) with 362 visits (14%), genital or sexual complaints (as detailed in the introduction) caused 362 visits (11.3%), psychological symptoms (anxiety, depression) 359 visits (11.3%), hot flushes 346 visits (10.8%), disorders of the metabolism 342 visits (10.7%), urinary infections 283 visits (8.9%) and other motives which do not come into the previous categories with a total of 188 visits (5.9%). In 8.3% of the total number of visits the motive for the consultation does not figure in the patient's clinical record.

74.6% of the climacteric women were referred to a specialist at some time, with an average of 1.7 referrals per woman and year. Routine screening in this age group, such as cervical smears or mammographies were not included.

Of the total number of referrals, the highest percentage were due to rheumatic causes which caused 28,125, followed by genital complaints 23%, metabolism disorders 14.3%, cardiovascular problems 14.1%, psychological complaints 12.5%, urinary infections 7.1% and other reasons 1%.

Table 1. Reasons for consultation with a family doctor by the climacteric women (n = 291)

Symptoms	N	%
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These percentages can be misleading, because when we calculate the rate of referrals according to symptoms (the frequency of referral for each reason for every 100 consultations for the same reason) as is shown in Table 2, we find that the consultations made for genital and/or sexual problems lead to the highest number of referrals, 32%, followed by rheumatic symptoms 24%, metabolism disorders 21.1% and psychological problems 17.6%.

Overall, as was previously mentioned, three levels were established to reflect the women's level of knowledge about the climacteric, according to their answers to the questions shown in Figure 2. 42.8% of the women were found to have a high level of knowledge, 40.6% a medium level and 16.6% a low level.

One of the questions which figured in the questionnaire to ascertain the level of knowledge was to determine if the climacteric women knew of the existence of hormone replacement therapy (HRT). 61% claimed to know of it but only 30% of the women questioned had requested the treatment.

No statistically significant difference was found to relate the level of the women's knowledge about the climacteric and the degree of use of the health services.

On the other hand there was an appreciably significant statistical difference in the age and educational level of the women related to their knowledge about the climacteric: the higher the educational level and the younger the woman ($p < 0.05$), the higher the level of knowledge was about the climacteric ($p < 0.001$).

Finally, it was observed that 65.7% of the women felt that their families were supportive and when they were supported they showed less psychological problems and, consequently, the less they consulted their doctor for this reason ($p < 0.00001$).

Discussion

The average age of the women in the climacteric phase obtained at the Basic Health Zone studied is similar to that described by the majority of authors, who find that it occurs at fifty years of age, with a

Table 2. Referrals

Cause	%	Rate ^a
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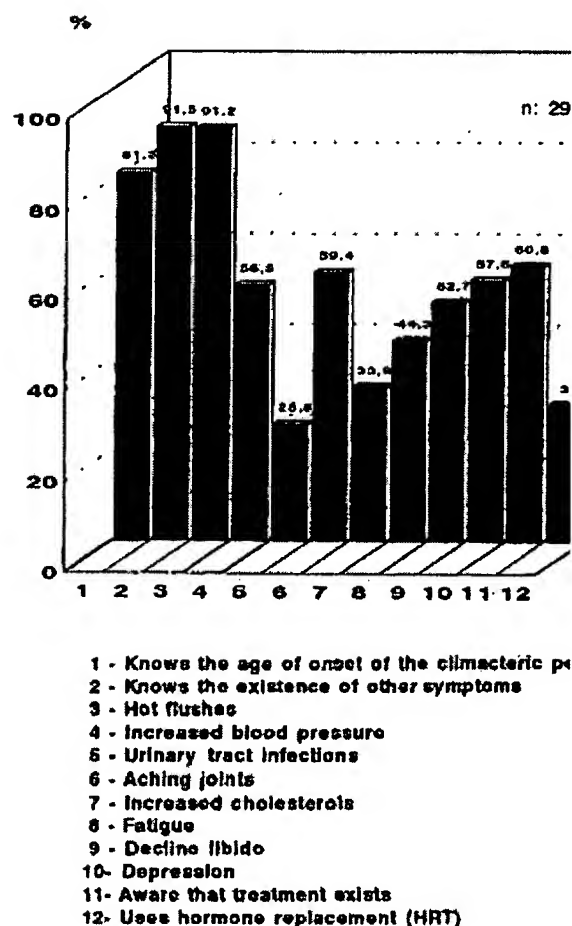


Figure 2. Symptoms and knowledge about the climacteric syndrome among climacteric women in the population sample.

standard deviation of 1.5 years [1]. This is slightly higher than that found by Mayer and Linsco Hughes [9], Comino [2] and the Spanish Society of Gynaecology and Obstetrics, which varies from 45 to 47 years in the last case [4].

Although the great use of the health services by a part of this group of women has been pointed out by authors such as Barlow and Borrell [10, 11] this has not been correlated with the use of services by the remaining groups of women.

The principal motives for which the climacteric women in our Basic Health Zone consulted their doctor were comparable with the findings of Barlow and Jiménez de Luque [12] among others, the frequent reasons were symptoms associated with the climacteric: rheumatic, cardiovascular, genital and sexual problems. It has not been our concern in this study, as has been the case with some other authors [13] to co-

educational level have a significant influence on the magnitude of the problem; following this line, we have found no studies which consider the possible relation between these variables and the use of the health services.

There was a strikingly high percentage of women who had no schooling (28.5) and of women with only primary education (41%). This is in fact typical for middle-aged women in most rural areas in Spain, due to the economic depression after the Spanish civil war that did not encourage women's education. The situation is very different today thanks to compulsory education and a change of mentality in relation to women.

The results obtained for the symptoms identified with the climacteric period by the women in our sample were observed to be similar to those of Mayer and Linscott [8], Randall [14] and Barlow [10] who found hot flushes and aching joints as the most frequently symptoms identified by the climacteric women.

Tropeano et al. [15] and Tejerizo [16] give particular importance to the fact that the women who felt that their families gave them support and understanding appeared to have less problems of a psychological nature and ask for less help for these motives. This is in consistence with the results obtained in our study.

Conclusions

1. The use of the health services by the climacteric women of the Rodríguez Arias Basic Health Zone in San Fernando (Cádiz) during 1995 was significantly superior to that of non-climacteric women for the same period of time.
2. The principal motives for consultation were rheumatic, followed by cardiovascular and genital and/or sexual problems.
3. There is a statistically significant relation between the use of the health services by climacteric women and their educational level and age.
4. There is a high degree of referral to second or third degree health care for the climacteric women who used the health services.
5. The climacteric women in the Rodríguez Arias Health Zone in San Fernando (Cádiz) have a medium-high level of knowledge about the climacteric process. Younger women, with a higher educational level, have more knowledge about the

level of Primary Health Care. This is a possibility which is included in the Spanish legislation through the Government Health Programme of the Autonomy of Andalusia, but which has not yet been put into practice. However, in view of daily experience, the results of this study and the recommendations of a number of different authors [17-20], the present authors feel that a plan of action should be designed with three main objectives: To create a mechanism which provides for the health care of the climacteric woman in the Basic Health Zone (BHZ) within the Health Centre: A Primary Health Care Menopause Unit (PHCMU). This would be made up of a multidisciplinary team consisting of a family doctor, nurses, a social worker and a psychologist.

To give counselling in the family environment to the climacteric woman of the BHZ under the care of the Unit, in those cases where it is considered to be prejudicial to the psychological welfare of the woman.

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